

APRIL 15

1991

COK-1101290-27-P024328

AMERICAN JOURNAL OF OPHTHALMOLOGY

27

Monthly since 1884

• ORIGINAL ARTICLES

Epikeratoplasty in Children

Armesto, Lee, Prager, Goosey, Goosey

Congenital Homonymous Hemianopsia

Bosley, Kiyosawa, Moster, Harbour, Zimmerman, Savino, Sergott, Alavi, Reivich

Variable Expression of Albinism

Castronuovo, Simon, Kandel, Morier, Wolf, Witkop, Jenkins

Loss of Contrast Sensitivity in Cystic Fibrosis

Leguire, Pappa, Kachmer, Rogers, Bremer

Scleritis and Wegener's Granulomatosis

Sacks, Stock, Crawford, Greenwald, O'Grady

Nuclear Sclerosis After Vitrectomy

Cherfan, Michels, de Bustros, Enger, Glaser

Ultrastructure of Norrie's Disease

Enyedi, de Juan, Gaitan

S Cones and Goldmann-Favre Syndrome

Jacobson, Román, Román, Gass, Parker

Retinitis Pigmentosa and Severe Hyperopia

Lam, Judisch

Corneal Ulcer and Contact Lens Studies

MacRae, Herman, Stulting, Lippman, Whipple, Cohen, Egan, Wilkinson, Scott, Smith, Phillips

Keratitis and Cyanoacrylate Adhesive

Cavanaugh, Gottsch

Cell-Mediated Immunity in Blepharitis

Ficker, Ramakrishnan, Seal, Wright

Herpes Simplex Dendritic Keratitis After Keratoplasty

Mannis, Plotnik, Schwab, Newton

Initial Abnormalities of Glaucoma

Tuulonen, Airaksinen

Visual Field Loss in Glaucoma

O'Brien, Schwartz, Takamoto, Wu

Silicone Oil Pupillary Block

Bartov, Huna, Ashkenazi, Melamed, Gutman, Naveh, Treister

Nd:YAG Iridotomy and Corneal Endothelium

Panek, Lee, Christensen

• EDITORIALS

A Plea for Low Tech

Kramer

Senile Accommodative Degeneration (SAD)

Jampolsky

• LETTERS TO THE JOURNAL

Sector palsy of pupil after trabeculoplasty

Pfeiffer, Kommerell

Recurrent hyphemas in pseudophakia

Geisse

Pain from intraocular lens loop

Legler, Apple, Hund, Kirkconnell

Uveitis and swollen tattoos

Mansour, Chan

Vertebral artery occlusion and perimetry

De Keyser, Herroelen, Van Langenhove

Terrien's marginal degeneration

Kremer

Amiodarone in corneal deposits

Haug, Friedman

Ophthalmomyiasis with *Cochliomyia macellaria*

Chodosh, Clarridge, Matoba

Proteus syndrome

Lessner, Margo

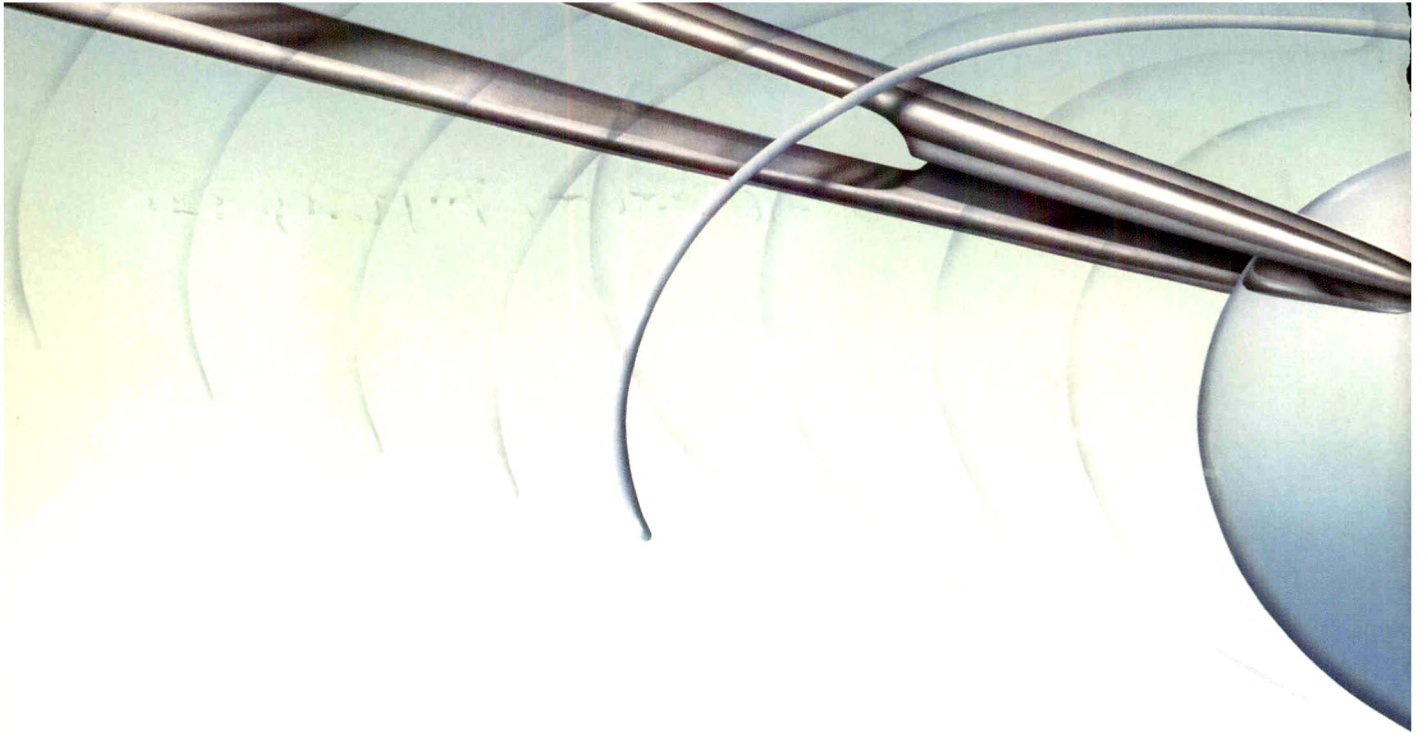
Ichthyosis and crystalline maculopathy

Teske, Reid, Tweeten, Swartz


Blepharoptosis and systemic thymoxamine

Chitkara, Hudson

AJO®



Viscoelastic
penetration
this dynamic is
the newest thing
you'll notice



Introducing The Storz Financial Services Group

You have known Storz for years—now we can offer you more. In the past, Storz has always provided ophthalmologists with superior products and service.

Today, that's not enough. The current medical and financial climate presents a new set of challenges. Now Storz introduces a series of sound financial programs specifically designed to meet those challenges and overcome the economic obstacles facing today's practicing ophthalmologist.

Featuring Practice Investment Plus

At Storz, we understand the special financial demands of a competitive ophthalmic practice. That's why we want to work with you to attain the competitive edge. Our Practice Investment Plus program allows you to easily finance the PREMIERE™ phacoemulsification system—or any other acquisition you need to meet the high standards you set for your practice. This is just one example of the Storz investment in you.

Commitment to the Best

The Storz commitment to ophthalmology is based on our 100-year tradition of quality. We know our success is possible only through your success—and we aspire to be a valued resource for your professional and economic growth. Backed by the corporate support of American Cyanamid, a respected name worldwide, we will continue to put our quality and innovation into practice. More importantly, into your practice.

Call 1-800-325-9500 for more information.



FINANCIAL SERVICES GROUP

We mean business.™

P 24,328

AJO®

AMERICAN JOURNAL OF OPHTHALMOLOGY®

ISSN 0002-9394

April 1991

Series 3, Vol. 111, No. 4

OPHTHALMIC PUBLISHING COMPANY

EDWARD W. D. NORTON, *President*
BRADLEY R. STRAATSMAN, *Vice President*
FRANK W. NEWELL, *Secretary and Treasurer*
BRUCE E. SPIVEY, *Director*
THOMAS M. AABERG, *Director*
MICHAEL A. KASS, *Director*
MARY L. BORYSEWICZ, *Assistant Secretary and Assistant Treasurer*

AMERICAN JOURNAL OF OPHTHALMOLOGY®

FRANK W. NEWELL, *Publisher and Editor-in-Chief*
H. STANLEY THOMPSON, *Book Review Editor*
THOMAS M. AABERG, *Senior Associate Editor*
MICHAEL A. KASS, *Abstract Editor*
FRED EDERER, *Associate Editor*

EDITORIAL BOARD

Jules Baum, <i>Boston</i>	Allen M. Putterman, <i>Chicago</i>
William M. Bourne, <i>Rochester</i>	Dennis Robertson, <i>Rochester</i>
Ronald M. Burde, <i>New York</i>	Merlyn M. Rodrigues, <i>Baltimore</i>
Frederick T. Fraunfelder, <i>Portland</i>	Stephen J. Ryan, <i>Los Angeles</i>
Steven G. Kramer, <i>San Francisco</i>	Jerry A. Shields, <i>Philadelphia</i>
Irving H. Leopold, <i>Irvine</i>	M. Bruce Shields, <i>Durham</i>
Robert Machemer, <i>Durham</i>	Ronald E. Smith, <i>Los Angeles</i>
Nancy M. Newman, <i>San Francisco</i>	Bruce E. Spivey, <i>San Francisco</i>
Don H. Nicholson, <i>Miami</i>	Bradley R. Straatsma, <i>Los Angeles</i>
Edward W. D. Norton, <i>Miami</i>	E. Michael Van Buskirk, <i>Portland</i>
Deborah Pavan-Langston, <i>Boston</i>	Gunter K. von Noorden, <i>Houston</i>

GENERAL INFORMATION

Address typescripts to Frank W. Newell, M.D., Editor, AMERICAN JOURNAL OF OPHTHALMOLOGY, Suite 1415, 435 North Michigan Avenue, Chicago, IL 60611.

At the time of submission, a copyright transfer, published monthly in THE AMERICAN JOURNAL OF OPHTHALMOLOGY, signed by each of the authors must be included with the typescript. No article or letter will be reviewed until the signed copyright transfer is received.

Manuscripts must be original material submitted solely to THE AMERICAN JOURNAL OF OPHTHALMOLOGY. Two copies must be submitted; the second copy may be machine-duplicated. The entire manuscript, including case reports, footnotes, and references, must be typed double-spaced, with 1½-inch margins, on 8½ by 11-inch heavy white bond paper. See Instructions to Authors published elsewhere in this issue. Copies of Instructions to Authors will be mailed on request. All manuscripts originating in the United States must be sent by first-class mail; those manuscripts originating outside the United States must be sent airmail. Receipt of manuscript is acknowledged immediately.

Manuscripts submitted for consideration are reviewed by members of the Editorial Board and other experts in the field. An unpublished manuscript is a privileged document that must be protected from any form of exploitation. The reviewer should not cite the manuscript or refer to the work it describes before it has been published. Reviewers must refrain from using the information contained in the manuscript for the advancement of their own work, their colleagues' work, or their institution's work. Reviewers are consultants to the editor and are instructed not to discuss the paper with the authors. Reviewers work anonymously and their identity may not be revealed to authors or to others.

Edited typescripts sent to the author must be corrected and returned within 48 hours to Manuscript Editor, AMERICAN JOURNAL OF OPHTHALMOLOGY, Suite 1415, 435 North Michigan Avenue, Chicago, IL 60611.

Permission to reprint any portion of published articles must be obtained in writing from both the Ophthalmic Publishing Company and from the authors of the articles.

Reprints may be obtained from Ophthalmic Publishing Company, Suite 1415, 435 North Michigan Avenue, Chicago, IL 60611, if ordered at the time the typescript is returned.

Address news items and society proceedings to News Editor,

AMERICAN JOURNAL OF OPHTHALMOLOGY, Suite 1415, 435 North Michigan Avenue, Chicago, IL 60611.

Subscriptions: Subscriptions, requests for single issues, notices of change of address, advertising and other communications should be sent to Ophthalmic Publishing Company, Suite 1415, 435 North Michigan Avenue, Chicago, IL 60611. Notices of change of address must be received at least 60 days in advance and must include both old and new addresses and AJO identification number.

Send claims for issues not received no later than two months after the issue date for domestic and Canadian subscribers and four months after the issue date for all other foreign subscribers. Address claims to Circulation Coordinator, Ophthalmic Publishing Company, Suite 1415, 435 North Michigan Avenue, Chicago, IL 60611.

Advertising: Insertion orders, copy, and materials should be sent to the Media Planner and must be received by the 20th of the second preceding month that the advertisement is scheduled. Consult the Advertising Department for extensions, rates, and media kits at THE AMERICAN JOURNAL OF OPHTHALMOLOGY, Suite 1415, 435 North Michigan Avenue, Chicago, IL 60611; telephone (312) 787-3853; FAX (312) 787-5186.

THE AMERICAN JOURNAL OF OPHTHALMOLOGY is published monthly by the Ophthalmic Publishing Company, Suite 1415, 435 North Michigan Avenue, Chicago, IL 60611. The subscription rates in the United States are as follows: one-year individual \$52, institution \$73; two-year individual \$98, institution \$136. In Canada and all other foreign countries, the rates are as follows: one-year individual \$80, institution \$113; two-year individual \$150, institution \$210; paid in U.S. bank draft or international money order. Single issues are available for \$15.00 in the United States and for \$20.00 in all other countries. Subscription and Advertising Office: Ophthalmic Publishing Company, Suite 1415, 435 North Michigan Avenue, Chicago, IL 60611.

© 1991, Ophthalmic Publishing Company. Second class postage paid at Chicago, Illinois, and at additional mailing offices. Printed in U.S.A. POSTMASTER: Send address changes to Ophthalmic Publishing Co., Suite 1415, 435 North Michigan Avenue, Chicago, IL 60611.



AJO is a registered service mark of the Ophthalmic Publishing Company.

Evaluate Macular Function - Immature cataracts require the most precise potential acuity testing . . .

MENTOR® Guyton-Minkowski PAM™ Potential Acuity Meter

■ Clinically Proven Accuracy

- Quantitative measurement using Snellen letter chart and/or number chart with sizes ranging from 20/400 to 20/20.
- Accurate 95% of the time preoperatively to within one line of post-op acuity when prediction is 20/40 or better.
- Spherical correction adjustable from - 10D to +13D.

■ Simple to Use, Fast

- Mounts on Slit Lamp for stability, mobility and comfort.
- Red background illumination light facilitates positioning in darkened lane, or with dark irises.
- Test can be performed on a dilated pupil in less than 3 minutes.

■ Other Uses

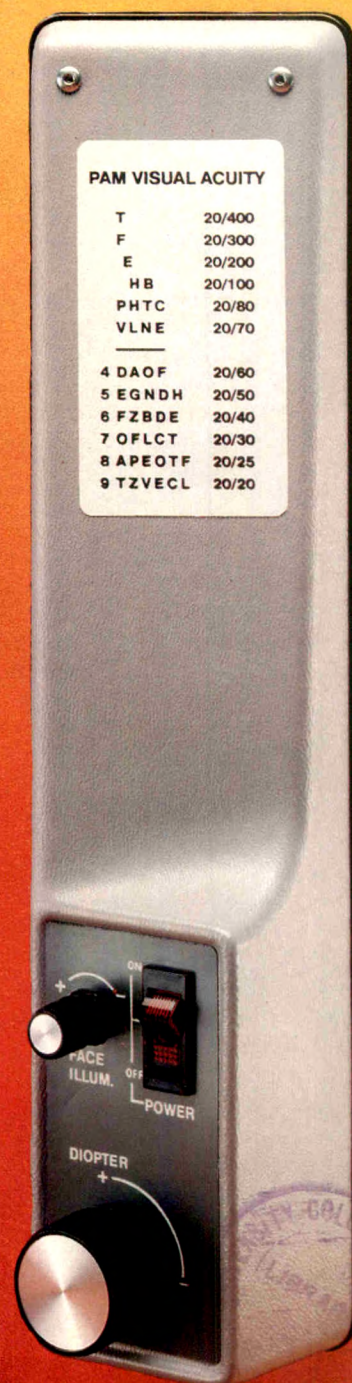
- Testing retinal acuity in presence of other media problems.
- Rapid vision screening for retinal patients.
- Rapid screening of literate children with large refractive errors.
- Rapid retinal vision testing without refraction in post-surgical cases.

To place an order, arrange a demonstration, or obtain more information, please write or call:

1-800-992-7557

1-617-871-6950

MENTOR® and PAM are trademarks of Mentor O & O, Inc.



PAM VISUAL ACUITY

T	20/400
F	20/300
E	20/200
HB	20/100
PHTC	20/80
VLNE	20/70
<hr/>	
4 DAOF	20/60
5 EGNDH	20/50
6 FZBDE	20/40
7 OFLCT	20/30
8 APEOTF	20/25
9 TZVECL	20/20

MENTOR O&O INC.

3000 Longwater Drive, Norwell, MA 02061-1610

TABLE OF CONTENTS

ORIGINAL ARTICLES

Epikeratoplasty with nonlyophilized tissue in children with aphakia

David M. Armesto, Andy M. Lee, Thomas C. Prager, Claire B. Goosey, and John D. Goosey 407

Neuro-imaging and positron emission tomography of congenital homonymous hemianopsia

Thomas M. Bosley, Motohiro Kiyosawa, Mark Moster, Robert Harbour, Robert Zimmerman, Peter J. Savino, Robert C. Sergott, Abass Alavi, and Martin Reivich 413

Variable expression of albinism within a single kindred

Susan Castronuovo, John W. Simon, Gillray L. Kandel, Albert Morier, Bruce Wolf, Carl J. Witkop, and Paul L. Jenkins 419

Loss of contrast sensitivity in cystic fibrosis

Lawrence E. Leguire, Karl S. Pappa, Mary Lou Kachmer, Gary L. Rogers, and Don L. Bremer 427

Scleritis and Wegener's granulomatosis in children

Robert D. Sacks, E. Lee Stock, Susan E. Crawford, Mark J. Greenwald, and Richard B. O'Grady 430

Nuclear sclerotic cataract after vitrectomy for idiopathic epiretinal membranes causing macular pucker

George M. Cherfan, Ronald G. Michels, Serge de Bustros, Cheryl Enger, and Bert M. Glaser 434

Ultrastructural study of Norrie's disease

Laura Barlow Enyedi, Eugene de Juan, Jr., and Alicia Gaitan 439

Relatively enhanced S cone function in the Goldmann-Favre syndrome

Samuel G. Jacobson, Alejandro J. Román, Marisa I. Román, J. Donald M. Gass, and John A. Parker 446

Early-onset autosomal dominant retinitis pigmentosa with severe hyperopia

Byron L. Lam and G. Frank Judisch 454

Corneal ulcer and adverse reaction rates in premarket contact lens studies

Scott MacRae, Carol Herman, R. Doyle Stulting, Richard Lippman, David Whipple, Elisabeth Cohen, Donald Egan, Charles P. Wilkinson, Clifford Scott, Ronald Smith, and Dave Phillips 457

Infectious keratitis and cyanoacrylate adhesive

Timothy B. Cavanaugh and John D. Gottsch 466

Role of cell-mediated immunity to staphylococci in blepharitis

Linda Ficker, Meenakshi Ramakrishnan, David Seal, and Peter Wright 473

Herpes simplex dendritic keratitis after keratoplasty

Mark J. Mannis, Ronald D. Plotnik, Ivan R. Schwab, and R. Dale Newton 480

Initial glaucomatous optic disk and retinal nerve fiber layer abnormalities and their progression

Anja Tuulonen and P. Juhani Airaksinen 485

Intraocular pressure and the rate of visual field loss in chronic open-angle glaucoma

Colm O'Brien, Bernard Schwartz, Takenori Takamoto, and Da Ching Wu 491

Identification, prevention, and treatment of silicone oil pupillary block after an inferior iridectomy

Elisha Bartov, Ruth Huna, Isaac Ashkenazi, Shlomo Melamed, Isaac Gutman, Nava Naveh, and Giora Treister 501

The effects of Nd:YAG laser iridotomy on the corneal endothelium

William C. Panek, David A. Lee, and Robert E. Christensen 505

EDITORIALS

A plea for low tech

Steven G. Kramer 508

Senile accommodative degeneration (SAD)

Arthur Jampolsky 510

LETTERS TO THE JOURNAL

Sector palsy of the sphincter pupillae muscle after argon laser trabeculoplasty. Norbert Pfeiffer and Guntram Kommerell, 511. **Nd:YAG laser treatment for recurrent hyphemas in pseudophakia.** Lawrence J. Geisse, 513. **Chronic ciliary pain secondary to posterior chamber intraocular lens loop incarceration.** Ulrich F. C. Legler, David J. Apple, Paul Hund, and Waite S. Kirkconnell, 513. **Recurrent uveitis preceded by swelling of skin tattoos.** Ahmad M. Mansour and Chi-Chao Chan, 515. **Vertebral artery occlusion complicating perimetry.** Jacques De Keyser, Luc Herroelen, and Luc Van Langenhove, 516. **Terrien's marginal degeneration associated with vernal conjunctivitis.** Israel Kremer, 517. **Identification of amiodarone in corneal deposits.** Stephen J. Haug and Alan H. Friedman, 518. **Nosocomial conjunctival ophthalmomyiasis with *Cochliomyia macellaria*.** James Chodosh, Jill E. Clarridge, and Alice Matoba, 520. **Eyelid tumors in the proteus syndrome.** Alan Lessner and Curtis E. Margo, 521. **Ichthyosis and crystalline maculopathy.** Michael P. Teske, Thomas K. Reid, James P. Tweeten, and Mano Swartz, 522. **Blepharoptosis caused by systemic thymoxamine.** Deepak

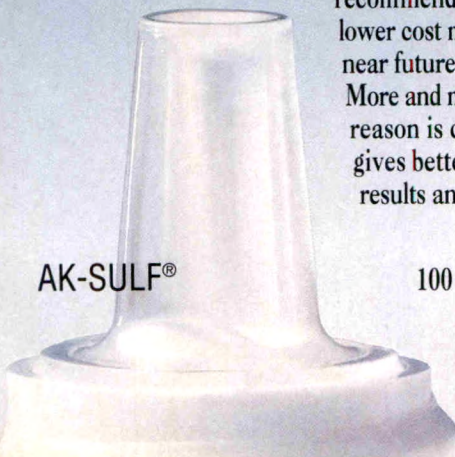


Akorn

**TOPS THEM ALL
WITH COMPLYING
COLORS**

When the American Academy of Ophthalmology requested pharmaceutical manufacturers to provide color-coded caps with all ophthalmic preparations, AKORN responded immediately. That's why AK-Sulf and AK-Pred are available with the tan and pink caps according to the AAO's recommendations. And the rest of AKORN's line of quality, lower cost medications will have color-coded caps in the very near future.

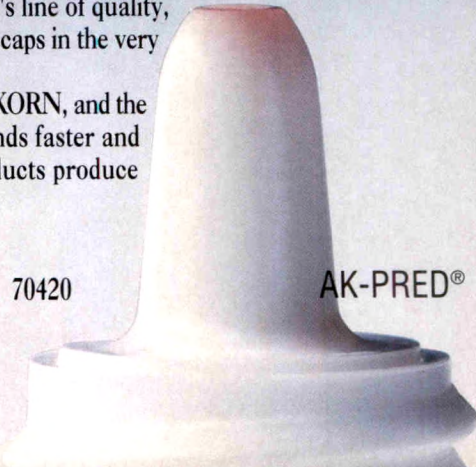
More and more physicians are prescribing AKORN, and the reason is clear. No other company responds faster and gives better service. AKORN... our products produce results and reduce costs. That's a promise.



AK-SULF®

Akorn, Inc.
100 Akorn Drive, Abita Springs, LA 70420
1-800-535-7155
In Louisiana 1-800-344-2291
FAX 504-893-1257

NASDAQ Symbol: AKRN



AK-PRED®

TABLE OF CONTENTS (continued from Advertising page 6)

K. Chitkara and John M. Hudson, 524. Vitreous Float-
er. Bernadine Z. Paulshock, 525.

CORRESPONDENCE

The natural course of central retinal vein occlusion.
L. L. Hansen and J. Wiek, 525. Treatment of traumatic
optic neuropathy with corticosteroids. Thomas C.
Spoor, Walter C. Hartel, Daniel B. Lensink, and Michael
J. Wilkinson, 526.

BOOK REVIEWS

Manual of Visual Fields (Elliot B. Werner). Reviewed
by William M. Hart, Jr., 527. Age-Related Cataract
(Richard W. Young), 527. Practical Management of
Squint (Graham Pittar), 527.

ABSTRACTS 528

NEWS ITEMS 537

CLASSIFIEDS Begins on Advertising 69

COPYRIGHT TRANSFER Advertising 16

INSTRUCTIONS TO AUTHORS Advertising 45

PRODUCTS AND SERVICES Begins on Advertising 58

ADVERTISING INDEX Advertising 71

PUBLICATION STAFF

MARY L. BORYSEWICZ
Executive Managing Editor

LINDA G. CLAUSEN
Records Manager

KAREN D. JOHNSON
Manuscript Editor

MOLLY MELICK
Assistant to the Editor

DIANN J. MARQUIS
Editorial Assistant

MICHAEL J. LUND
Subscription Correspondent

LYNN ANN LINDVIG
AND
RENEE L. KASTAR
Sales and Production

Epikeratoplasty With Nonlyophilized Tissue in Children With Aphakia

David M. Armesto, M.D., Andy M. Lee, B.A., Thomas C. Prager, Ph.D.,
Claire B. Goosey, M.S., and John D. Goosey, M.D.

We studied 75 epikeratoplasty procedures using nonlyophilized tissue performed by eight ophthalmic surgeons in 70 eyes (47 patients) to correct for aphakia in children less than 8 years of age (mean age, 3.4 ± 2.1 years). Of the 47 patients in the study, 24 were girls and 23 were boys; 23 patients had bilateral surgery. Seven of the epigrafts required removal; two were not replaced, and five underwent successful repeat epikeratoplasty. Overall, the success rate (that is, the percentage of epigrafts that remained optically and functionally clear throughout the course of this study) for the epikeratoplasty procedure was 89% (62 of 70 eyes) for initial surgery and 96% (67 of 70 eyes) for repeat surgery. The average spherical equivalent was $+14.4 \pm 3.7$ diopters preoperatively and $+0.3 \pm 2.9$ diopters one year after the operation. One year after the final surgical procedure, 42 of 56 eyes (75%) were within 3 diopters of emmetropia. In the 29 verbal patients, best-corrected visual acuity was 20/100 or better in 25 (86.2%) one year after the operation.

THE VISUAL REHABILITATION of children with aphakia remains one of the most challenging clinical problems in ophthalmology. Without accurate optical correction and diligent amblyopic therapy, the prognosis for good visual acuity is extremely poor. The alternatives for aphakic correction include spectacles, contact lenses, intraocular lenses, and epikeratoplasty.¹ Although spectacles are useful for children

with bilateral aphakia, they are rarely successful in patients with unilateral aphakia because of the associated anisometropia and aniseikonia. Contact lenses provide a superior optical solution for correcting aphakia in children, and compliance with contact lenses is usually good during the first 12 to 18 months of life. After this time period, problems with compliance usually begin as the child becomes more active and can dislodge the contact lens. This may lead to unknown time periods of visual deprivation, which increase the likelihood of amblyopia. After multiple contact lenses are lost, even the most dedicated parents can become frustrated with the treatment guidelines necessary to prevent amblyopia.

Before epikeratoplasty, children who were spectacle- and contact lens-intolerant were left with the option of an intraocular lens implantation. Secondary intraocular lens implantation may provide rapid visual rehabilitation,² but this procedure is also associated with numerous serious complications, including infectious endophthalmitis, persistent uveitis-glaucoma-hyphema syndrome, retinal detachment, and corneal edema.^{3,4} In contrast, epikeratoplasty has been shown to be a safe and effective treatment for aphakia in children.⁵⁻¹⁰

The rapid restoration of refractive error and media clarity are critical components to the successful rehabilitation of aphakia in children. The nationwide study of epikeratoplasty for aphakia in children^{8,9} reported the results of 97 surgeons who performed a total of 335 procedures. The accuracy of the procedure was analyzed in 151 patients and disclosed that 73% were within 3 diopters of emmetropia postoperatively.⁹ Other studies on epikeratoplasty have reported the results of epikeratoplasty with corneal tissue that has been lyophilized. It has been noted that one of the major clinical complications after epikeratoplasty is related to problems of reepithelialization of the graft surface. It has been suggested that present methods of tissue preparation may be deleteri-

Accepted for publication Jan. 9, 1991.

From the Department of Ophthalmology, University of Texas Medical School, and Hermann Eye Center, Houston, Texas. Dr. Goosey has a proprietary interest in Cryo-Optics, Inc., Houston, Texas.

Reprint requests to David M. Armesto, M.D., Department of Ophthalmology, Hermann Eye Center, 6411 Fannin, Houston, TX 77030.

ous to the structure of the lenticule and therefore compromise reepithelialization.¹¹⁻¹³ We examined the efficacy of epikeratoplasty using nonlyophilized corneal tissue in children with aphakia as it relates to graft survival and refractive results.

Patients and Methods

Between Sept. 10, 1984, and March 14, 1990, 70 eyes underwent epikeratoplasty for the correction of surgical aphakia. All patients were at least 13 months of age, had no corneal scarring, and were intolerant of contact lenses and spectacles. No children had additional procedures other than epikeratoplasty. Of the 47 patients, 32 (68%) had congenital cataracts, eight (17%) had developmental cataracts, and seven (15%) had traumatic cataracts. Twenty-three children had bilateral surgery. The average age of the study population was 3.4 ± 2.1 years (range, 1 to 7 years) and consisted of 23 boys and 24 girls. Tissue lenses were removed from eight eyes, and five of these underwent repeat epikeratoplasty. Of the total 75 procedures performed, 57 patients (76%) have had more than 12 months of postoperative follow-up.

The epikeratoplasty procedure involves freezing a donor cornea and lathing it to the appropriate optical correction based on the patient's preoperative keratometry measurements and refractive error. After the lens is cryolathed, it can either be stored in a wet nonfrozen state (McCarey-Kaufman medium or moist pack) or lyophilized. This prelathed piece of human corneal tissue (lenticule) is then placed onto the surface of the patient's cornea and sutured into place. The lenticule is gradually repopulated with the host keratocytes and becomes a living contact lens,¹⁴ which decreases the anterior radius of curvature of the patient's eye and thereby corrects the aphakic refractive error.

In our technique, we eliminated the lyophilization process in tissue preparation. Human corneal tissue was initially processed in a corneal press to restore the tissue to a uniform hydration state. The tissue was then frozen and lathed on a Barraquer cryolathe to form a plus-power lenticule. The desired lenticule power was calculated using the patient's preoperative refractive error and keratometry measurements. The central thickness of the lenticule varied depending on refractive power. The

overall lenticule diameter was always 9.0 mm. The lenticule was stored in McCarey-Kaufman medium for no longer than 72 hours before surgery.

The surgical technique consisted of mechanical débridement of the central 9.0 to 10.0 mm of the recipient corneal epithelium. If the epithelium was too difficult to remove, alcohol- or cocaine-soaked cellulose sponges were used to loosen the epithelium. Epithelial débridement was followed by trephination with a 7.0-mm, single-blade, Hessburg-Barron vacuum trephine to a depth of approximately 0.25 mm. The diameter of the trephine was 2.0 mm smaller than the diameter of the lenticule. A peripheral lamellar pocket was created 2.0 mm from the outer aspect of the trephination, which extended 360 degrees. The lenticule was sutured onto the patient's cornea with multiple interrupted 10-0 nylon sutures. After 16 sutures were placed, the wing of the lenticule was tucked into the previously prepared lamellar bed. The suture knots were rotated beneath the host side of the incision. A subtenon's injection of 40 mg of gentamicin sulfate was given. Atropine 1% eyedrops and gentamicin sulfate eyedrops were then added. The eye was closed with a cotton patch, and a protective shield was placed over the operated on eye. Postoperatively the children were examined daily until epithelialization was complete. Once the graft was epithelialized, pressure patching was discontinued and topical antibiotics were given three times per day for ten days. Suture removal was performed two to four weeks postoperatively, under general anesthesia in most cases.

Results

To assess the effectiveness of epikeratoplasty in the visual rehabilitation of pediatric patients who have aphakia, data were analyzed on Allen or Snellen visual acuity (when obtainable) and spherical equivalents obtained at one, two, three, four, six, 12, and 24 months postoperatively. Graft survival was also included as a means of evaluating the success of the procedure. Graft survival is defined as those grafts that remained clear throughout the course of the study and provided functional refractive results.

Of the 47 patients, 15 (32%) were preverbal, which limited assessment of visual acuity. However, visual acuity was measured on 32 of

TABLE 1
CORRECTED VISUAL ACUITY

	MONTHS POSTOPERATIVE					
	0	1	3	6	12	24
	(N = 21)	(N = 13)	(N = 17)	(N = 26)	(N = 29)	(N = 15)
	NO. %	NO. %	NO. %	NO. %	NO. %	NO. %
20/10–20/20	0 (0)	0 (0)	1 (5.9)	0 (0)	0 (0)	0 (0)
20/25–20/40	5 (23.8)	2 (15.4)	0 (0)	6 (23.1)	10 (34.5)	4 (26.7)
20/50–20/100	13 (61.9)	8 (61.5)	15 (88.2)	17 (65.4)	15 (51.7)	9 (60.0)
>20/100	3 (14.3)	3 (23.1)	1 (5.9)	3 (11.5)	4 (13.8)	2 (13.3)

47 patients (68%). Table 1 lists four categories of corrected visual acuity, 20/10 to 20/20, 20/25 to 20/40, 20/50 to 20/100, and 20/200 or worse, at different time points throughout the course of the study. At 12 months postoperatively, ten of 29 patients (34.5%) had visual acuity of 20/40 or better with correction, and 25 of 29 patients (86%) had visual acuity of 20/100 or better with correction. Only 12 eyes had visual acuity recorded both preoperatively as well as 12 months postoperatively, which made a complete analysis of visual acuity lost or gained over a one-year period limited. After one year, nine of these 12 eyes (75%) were within one line of their best-corrected preoperative visual acuity. The remaining three eyes lost two lines of visual acuity related to amblyopia.

Table 2 summarizes the number of eyes in four uncorrected visual acuity categories: 20/10 to 20/20; 20/25 to 20/40; 20/50 to 20/100; and 20/200 or worse. One year postoperatively, 28 of 29 eyes (97%) demonstrated improved uncorrected visual acuity. Two eyes (7%) had uncorrected visual acuity of 20/40 or better, and 20 (69%) had uncorrected visual acuity of 20/100 or better. This did not vary significantly at different time points in the study.

The mean and standard deviation for spherical equivalents both preoperatively and postoperatively are summarized in Table 3. The average preoperative spherical equivalent was +14.4 diopters (standard deviation, 3.7) in 68 patients. The mean spherical equivalent after one year was +0.26 diopters (standard deviation, 2.9) in 56 eyes, whereas at two years, the mean spherical equivalent was –0.19 diopters (standard deviation, 2.8) in 22 eyes. A multiple linear regression analysis over the one-year period did not demonstrate a significant pro-

gression toward myopia ($r = .15$, $F = 2.24$, $P = .14$). Table 4 shows data on the 16 patients who were available from preoperatively to 24 months postoperatively. A trend toward myopia with time was demonstrated. However, a multiple linear regression analysis over this two-year period again failed to demonstrate a significant linear regression of effect ($r = .25$, $F = 3.15$, $P = .08$).

At six months postoperatively, 43 of 52 eyes (83%) were within 3 diopters of emmetropia, and at 12 months, 42 of 56 eyes (75%) were within 3 diopters of emmetropia.

Twenty-three patients underwent bilateral epikeratoplasty; however, complete data were available on only 21 of these patients. Table 5 lists the spherical equivalents for 21 pairs of eyes. Of the 23 bilateral procedures, 22 (95%) had a refractive difference between the eyes of 3 diopters or less.

Seven corneal grafts were removed. Of these, five (71%) were removed because of epithelium in the interface. One graft had only minimal epithelial cysts in the interface but was removed because of overcorrection. Five of these grafts were replaced successfully. Two other

TABLE 2
UNCORRECTED VISUAL ACUITY

	MONTHS POSTOPERATIVE				
	1	3	6	12	24
	(N = 23)	(N = 23)	(N = 25)	(N = 29)	(N = 15)
	NO. %	NO. %	NO. %	NO. %	NO. %
20/10–20/20	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
20/25–20/40	1 (4.3)	1 (4.3)	2 (8.0)	2 (6.9)	3 (20)
20/50–20/100	12 (52.2)	17 (73.9)	17 (68)	18 (62.1)	8 (53)
>20/100	10 (43.5)	5 (21.7)	6 (24)	9 (31)	4 (27)

TABLE 3
SPHERICAL EQUIVALENTS (DIOPTERS)

	MONTHS POSTOPERATIVE					
	0 (N = 68)	1 (N = 41)	3 (N = 46)	6 (N = 52)	12 (N = 56)	24 (N = 22)
Mean	14.36	1.4	.95	.87	.26	-.19
Standard deviation	3.72	1.95	2.56	2.39	2.85	2.80
Median	13.75	1.5	.63	1.00	.00	.30
Range	6.50-24.75	-2.00-6.00	-5.00-7.50	-3.50-7.75	-5.50-7.50	-6.00-5.00

grafts were removed as a result of nonhealing epithelial defects. Neither of these grafts were replaced. Excluding those patients in whom the epithelium failed to heal, the average reepithelialization time was 3.8 ± 1.8 days. Visual acuity data were not available for grafts that were removed without replacement. None of these patients required further corneal surgery, such as a corneal transplant after removal of the epigraft, and there were no cases of damage to the underlying corneal host bed.

Discussion

The greatest shortcoming of the study is incomplete data collection with regard to visual acuity. Although 32 patients were verbal by the conclusion of the study, preoperative and postoperative visual acuity analysis, either with Snellen or Allen figures, was possible with only 12 eyes. Additionally, not all refractive data were collected for all postoperative time points, which limited somewhat the assessment of this factor.

It has been noted that epikeratoplasty procedures performed on children younger than 1 year of age show significant changes in refractive error with time and have unpredictable results.^{6,15,16} For this reason, no children young-

er than 1 year of age were candidates for this procedure. Our series demonstrates a stable refractive result over both a one- and two-year period, without significant progression toward myopia. The predictive ability of this procedure is best demonstrated in Table 5, which summarizes the refractive errors of each eye in those cases where bilateral surgery was performed. Of these 23 patients, 22 (95%) had 3 diopters or less of anisometropia, which reflects not only the accuracy of this procedure but also the desired capability that epikeratoplasty provides for the successful treatment of amblyopia. The accuracy of the procedure is further demonstrated in that 43 of 52 eyes (83%) were within 3 diopters of emmetropia at six months and 42 of 56 (75%) at 12 months. This does not compare as favorably with one other report, in which 55 of 57 eyes studied (97%) were within 3 diopters of emmetropia,¹⁷ but is better than other studies.^{5,9,10}

None of our patients were noted to have visual acuity loss of greater than two Snellen lines from preoperative measurements. Of the three patients in whom two lines were lost, two had unilateral aphakia and further development of amblyopia based on poor compliance with occlusion therapy. The other patient, with bilateral aphakia, had best-corrected preoperative visual acuity of R.E.: 20/400 and L.E.: 20/80. He underwent epikeratoplasty first in

TABLE 4
SPHERICAL EQUIVALENTS (DIOPTERS) OF 16 PATIENTS HAVING DATA AT ALL POSTOPERATIVE TIME POINTS

	MONTHS POSTOPERATIVE						
	0	1	3	6	9	12	24
Mean	13.86	1.90	1.30	2.04	1.42	.87	.16
Standard deviation	2.57	2.65	3.10	3.12	3.00	2.67	2.96
Median	13.00	2.00	.38	2.25	2.5	1.38	1.00
Range	10.25-18.50	-3.25-6.00	-3.38-7.50	-3.75-7.50	-4.38-4.00	-3.75-5.25	-6.0-5.0

TABLE 5
COMPARISON OF REFRACTION IN BILATERAL CASES

CASE NO.	R.E.	L.E.	ANISOMETROPIA
1	-2.25	0.00	2.25
2	-0.12	-1.25	1.13
3	-3.50	-3.50	0.00
4	1.25	0.75	0.50
5	1.75	1.50	0.25
6	3.00	3.00	0.00
7	3.00	-0.75	3.75
8	-0.50	-0.50	0.00
9	-1.50	1.25	2.75
10	1.00	0.00	1.00
11	3.25	2.00	1.25
12	-3.00	-1.00	2.00
13	5.25	4.50	0.75
14	-3.00	-3.50	0.50
15	0.75	1.00	0.25
16	3.62	5.25	1.63
17	-3.00	-3.00	0.00
18	-1.00	-0.75	0.25
19	7.50	7.50	0.00
20	0.00	-0.25	0.25
21	0.25	-0.13	0.38

the right eye, followed by epikeratoplasty to the left eye one month later. At 12 months after the second procedure, visual acuity was R.E.: 20/50 and L.E.: 20/200. The refractive error was -3.50 sphere in each eye. This further supports the important application that epikeratoplasty may have in the reversal of amblyopia based on its potential to provide excellent optical imaging to the visual cortex.

Graft survival and clarity are paramount to any other measure of success with epikeratoplasty. Since 1984, preparation of tissue for epikeratoplasty has typically involved lyophilization for storage and transportation. Binder and associates¹¹ in examining factory-prepared lenticules noted abnormalities in Bowman's membrane and in the structural integrity of the stromal matrix that were not noted in tissue stored in McCarey-Kaufman medium for two to four days or in corneas that were frozen. Binder¹³ later suggested that the technique of freezing and lathing was not solely responsible for the deleterious effect toward a rapid and permanent reepithelialization process. Indeed, the most commonly reported clinical problem requiring graft removal has been complications related to reepithelialization of the lenticule surface, ranging in occurrence from 38% to

45%.^{5,7,9,10} In two other studies using similar techniques,^{8,18} however, no graft failures were reported. This might suggest that factors other than tissue preparation may be causative, such as eye rubbing by the child with resultant epithelial defects and infections. One of these studies,⁸ however, reported on only a small patient population, whereas the other study⁸ examined children in an older age group.

In our series, seven graft failures occurred. The most common cause for graft failure was epithelium in the interface. Subsequent to this study, we have found that meticulous removal of epithelium is imperative to avoid this complication. Additionally, we have taken an extra measure to clean carefully the suture knot with an alcohol-soaked cellulose sponge before burying it. Care must be taken to use only a minimal amount of alcohol in this step, because this may lead to poor epithelial healing.

Only two cases of persistent epithelial defects were seen. There were no cases of graft melt. In one of these cases, the child had significant lagophthalmos and had difficulty using ointments. We did not replace the graft because of the high risk of poor epithelialization and possible repeat failure. In the other case, repeat grafting was not done because of lack of parental consent and the likelihood that good postoperative care would not be rendered. Of the five grafts that were replaced, all had a successful postoperative outcome. Overall, epikeratoplasty was successful in 62 of 70 eyes (89%) with initial surgery and in 67 of 70 eyes (96%) with repeat surgery.

Only two of seven graft failures (28%) resulted from poor epithelialization, which suggests that nonlyophilized tissue may provide a better outcome of success in graft survival. Other factors may be responsible, however, and only a comparative study of lyophilized and nonlyophilized tissue could reasonably answer this question. Although not quantifiable, it was the uniform impression of those surgeons who had the opportunity to work with both lyophilized and nonlyophilized tissue that the nonlyophilized tissue cleared much more quickly. We believe that this finding is of importance in children with aphakia whose critical period for the development of fixation is of limited duration. Not only does this procedure appear to provide for rapid clearing of media within the optical imaging system, but it allows maximally focused images to be projected onto the retina during the critical period of fixation development.

Although a favorable success rate was noted, the challenge of amblyopia therapy remains. Our findings confirm that epikeratoplasty provides an appropriate and excellent means by which to correct the optical error induced by surgical aphakia in children. Having achieved this, the management of the residual amblyopia is greatly simplified. Moreover, for those patients who are contact lens-intolerant, epikeratoplasty should be undertaken without delay to prevent permanent visual loss secondary to amblyopia.

References

1. Hiles, D. A.: Visual rehabilitation of aphakic children. *Surv. Ophthalmol.* 34:371, 1990.
2. ———: Visual acuity of monocular IOL and non-IOL phakic children. *Ophthalmology* 88:1296, 1981.
3. Hiles, D. A., and Hered, R. W.: Modern intraocular lens implants in children with new age limitations. *J. Cataract Refract. Surg.* 13:493, 1987.
4. Hiles, D. A.: Intraocular lens implantation in children with monocular cataract. *Ophthalmology* 91:1231, 1984.
5. Morgan, K. S., Arffa, R. C., Marvelli, T. L., and Verity, S. M.: Five year follow-up of epikeratophakia in children. *Ophthalmology* 93:423, 1986.
6. Arffa, R. C., Marvelli, T. L., and Morgan, K. S.: Keratometric and refractive results of pediatric aphakia. *Arch. Ophthalmol.* 103:1656, 1985.
7. Morgan, K. S., Stephenson, G. S., McDonald, M. B., and Kaufman, H. E.: Epikeratophakia in children. *Ophthalmology* 91:780, 1984.
8. Morgan, K. S., McDonald, M. B., Hiles, D. A., Aquavella, J. V., Durrie, D. S., Hunkeler, J. D., Kaufman, H. E., Keates, R. H., and Sanders, D. R.: The nationwide study of epikeratophakia for aphakia in older children. *Ophthalmology* 95:526, 1988.
9. ———: The nationwide study of epikeratophakia for aphakia in children. *Am. J. Ophthalmol.* 103:366, 1987.
10. Morgan, K. S., Asbell, P. A., McDonald, M. B., May, J. G., Loupe, D. N., and Kaufman, H. E.: Preliminary visual results of pediatric epikeratophakia. *Arch. Ophthalmol.* 101:1540, 1983.
11. Binder, P. S., Zavala, E. Y., Baumgartner, S. D., and Nayak, S. K.: The combined morphologic effects of cryolathing and lyophilization on epikeratoplasty lenticules. *Arch. Ophthalmol.* 104:671, 1986.
12. Rich, L. F.: Keratocyte survival in keratophakia lenticules. *Arch. Ophthalmol.* 99:677, 1981.
13. Binder, P. S.: Why do some epikeratoplasties fail? *Arch. Ophthalmol.* 105:63, 1987.
14. Kaufman, H. E.: The correction of aphakia. *Am. J. Ophthalmol.* 89:1, 1980.
15. Arffa, R. C.: Keratometric and refractive results of pediatric epikeratophakia. Effect of patient age. ARVO abstracts. Supplement to Invest. Ophthalmol. Vis. Sci. Philadelphia, J. B. Lippincott, 1985, p. 204.
16. Arffa, R. C., Marvelli, T. L., and Morgan, K. S.: Prediction of aphakic refractive error in children. *Ophthalmic Surg.* 18:581, 1987.
17. Uusitalo, R. J., and Lehtosalo, J.: Visual, refractive and keratometric results of epikeratophakia in children. *Arch. Ophthalmol.* 107:358, 1989.
18. Kelley, C. G., Keates, R. H., and Lembach, R. G.: Epikeratophakia for pediatric aphakia. *Arch. Ophthalmol.* 104:680, 1986.

Neuro-Imaging and Positron Emission Tomography of Congenital Homonymous Hemianopsia

Thomas M. Bosley, M.D., Motohiro Kiyosawa, M.D., Mark Moster, M.D.,
Robert Harbour, M.D., Robert Zimmerman, M.D., Peter J. Savino, M.D.,
Robert C. Sergott, M.D., Abass Alavi, M.D., and Martin Reivich, M.D.

Congenital homonymous hemianopsia is an uncommon asymptomatic visual field defect discovered typically in young adult life that is caused by a diverse group of insults to the retrochiasmal afferent visual system occurring prenatally, at birth, or during early childhood. We treated eight patients with congenital homonymous hemianopsia; seven with damage involving the optic radiations and one with an abnormality of the optic tract. We performed positron emission tomography using ^{18}F -fluoro-2-deoxyglucose on two patients with dense homonymous hemianopsias, lesions of the contralateral optic radiations, and largely intact occipital cortex. These studies showed minimal abnormalities in resting visual cortex glucose metabolism of the affected visual cortex.

IN 1976, Bajandas, McBeath, and Smith¹ reviewed the syndrome of congenital homonymous hemianopsia²⁻⁵ and described eight patients without severe neurologic signs or symptoms who had essentially asymptomatic homonymous visual field defects discovered by chance during childhood or young adult life.

These patients were examined before the widespread availability of computed tomography, magnetic resonance imaging, or positron emission tomography.

We treated eight patients with congenital homonymous hemianopsia examined with neuro-ophthalmic testing, visual field testing, and computed tomography. Three patients with normal computed tomographic scans were also studied with magnetic resonance imaging, and cerebral glucose metabolism was measured by positron emission tomography using ^{18}F -fluoro-2-deoxyglucose in two patients. The purposes of this study were to evaluate with computed tomography and magnetic resonance imaging the spectrum of anatomic lesions causing congenital homonymous hemianopsia and to estimate visual cortex metabolism in patients with largely intact primary visual cortex that has presumably been inactive since early childhood.

Patients and Methods

We studied eight patients (five males and three females ranging in age from 14 to 55 years; mean age, 35.5 years) who had asymptomatic homonymous visual field defects discovered by chance during childhood or young adult life. The patients were examined in neuro-ophthalmologic practices at Wills Eye Hospital, Temple University Hospital, and the Medical College of Georgia between 1983 and 1988. The patient in Case 3 has been previously described.⁶ These individuals were unaware that their vision was different, although in retrospect they often realized that they had more difficulty with sports or other visually guided activities. Patients were excluded from consideration if they were older than 40 years at the time visual loss was discovered or if they had a history of significant head trauma after

Accepted for publication Dec. 18, 1990.

From the Neuro-Ophthalmology Service, Wills Eye Hospital, Philadelphia, Pennsylvania (Drs. Bosley, Kiyosawa, Savino, and Sergott); Cerebrovascular Research Center (Dr. Reivich) and Department of Radiology (Drs. Zimmerman and Alavi), Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania; Department of Neurology, Temple University, Philadelphia, Pennsylvania (Dr. Moster); and Department of Ophthalmology, Medical College of Georgia, Augusta, Georgia (Dr. Harbour). This study was supported in part by Public Health Service program project grant NS-14867-09. Dr. Kiyosawa was supported by Fight for Sight Fellowship E-PD-100.

Reprint requests to Thomas M. Bosley, M.D., Neuro-Ophthalmology Service, Wills Eye Hospital, 9th and Walnut Sts., Philadelphia, PA 19107.

the age of 3 years, an acquired neurologic or ophthalmologic disease that might cause visual field loss, or a memory of visual field loss at any time.

A complete neuro-ophthalmic examination, Goldmann kinetic perimetry, and computed tomography were performed on each patient. Four patients had static visual perimetry, and three had magnetic resonance imaging performed on 1.5-T units. All computed tomographic and magnetic resonance imaging scans were reviewed by one of us (R.Z.).

Positron emission tomography was performed on two patients (Cases 1 and 2), each of whom had a complete left homonymous hemianopsia, right optic radiation damage on magnetic resonance imaging, and minimal anatomic changes in the occipital cortex on computed tomography and magnetic resonance imaging. The eyes were closed throughout the examination period beginning ten minutes before injection of 6 to 8 mCi of ^{18}F -fluoro-2-deoxyglucose. Each patient was then positioned with the head 20 degrees hyperextended from the orbitomeatal line in a modified version of the positron emission tomography scanner (PETT V).⁷ Data collection began 40 minutes after isotope injection, and brain images of local cerebral metabolic rates for glucose were obtained using the Phelps and associates⁸ modification of the method of Reivich and associates.⁹ Positron emission tomography was repeated on the patient in Case 1 after full visual field stimulation with a checkerboard pattern alternating at 5 Hz for 20 minutes before isotope injection and continuing for 60 minutes until the initiation of scanning.

Seven male volunteers aged 20 to 31 years were studied with positron emission tomography with eyes closed in a fashion identical to patients with congenital homonymous hemianopsia. These individuals had no neuro-ophthalmic complaints, visual acuity was 20/30 or better in each eye, and results of neurologic examinations were entirely normal. All patients and control subjects gave informed consent, and all procedures were approved by the Committee for Studies Involving Human Beings of the University of Pennsylvania.

Previous reports have described the characteristics of the positron emission tomography system, the data collection protocol,^{10,11} and the method used to derive global and regional cerebral metabolic rates for glucose.^{9,12} Metabolic regions of interest were placed by a computerized overlay system based on normal human anatomy as described previously.¹³

To reduce individual variability, the Laterality Index was calculated as described previously¹⁴ to compare metabolic rates in regions of the right cerebral hemisphere to homologous regions of the left hemisphere. Because of statistical limitations caused by the small number of patients, only four lobes and four regions of visual cortex were selected from each hemisphere for statistical evaluation by single sample *t*-test applying the Bonferroni correction for multiple tests. These regions were the frontal lobe, parietal lobe, temporal lobe, occipital lobe, anterior calcarine cortex, posterior calcarine cortex, peristriate cortex (Brodman's regions 18 and 19), and lateral occipital cortex (visual association cortex).

Results

The patient in Case 3 was born by forceps delivery, and the patients in Cases 5 and 8 had birth anoxia. The other five patients had no history of abnormal pregnancy, difficult delivery, or neurologic injury in the first years of life. No patient had epilepsy, mental retardation, psychosis, or other cognitive disturbances.

Table 1 shows pertinent portions of the neuro-ophthalmic examination. Visual acuity was better than 20/30 in at least one eye of all patients. Three patients had mildly decreased visual acuity in one eye caused by amblyopia associated with an exotropia. Five patients had right and three had left homonymous visual field defects. Six patients had complete homonymous hemianopsias, whereas two patients had incomplete hemianopsias.

Table 2 describes the results of computed tomographic and magnetic resonance imaging scans. All eight patients had computed tomographic scans, and the area of damage to the posterior afferent visual system was obvious in five patients (Cases 4 through 8). Computed tomographic scans appeared normal in three patients. One patient (Case 1) had magnetic resonance imaging evidence of damage to the optic radiations near the occipital horn of the right lateral ventricle. Another patient (Case 2) had a similar anatomic abnormality that also included the anterior occipital and posterior temporal lobes on the right (Fig. 1). One patient (Case 3) had a hypoplastic right optic tract on magnetic resonance imaging (Fig. 2).

Table 3 shows glucose metabolism in eight regions of interest of two patients (Cases 1 and 2) compared to seven control subjects. Cerebral

TABLE 1
RESULTS OF CLINICAL EXAMINATION IN EIGHT PATIENTS

CASE NO., AGE (YRS), SEX	VISUAL ACUITY		VISUAL FIELD	OPTIC DISK	EXTRAOCULAR MOTILITY	NEUROLOGIC SIGNS AND SYMPTOMS
	R.E.	L.E.				
1, 50, F	20/20	20/20	Complete left homonymous hemianopsia	Slight palor in both eyes	Normal	Normal
2, 46, F	20/25	20/20	Complete left homonymous hemianopsia	Hemioptic hypoplasia, L.E.	Exotropia	Migraine
3, 55, M	20/40	20/20	Complete left homonymous hemianopsia	Hemioptic hypoplasia, L.E.	Exotropia, congenital nystagmus	Sleep apnea
4, 49, M	20/25	20/15	Incomplete right homonymous hemianopsia	Normal	Normal	Trochlear nerve palsy
5, 19, F	20/25	20/25	Complete right homonymous hemianopsia	Hemioptic hypoplasia, R.E.	Normal	Normal
6, 14, M	20/50	20/25	Complete right homonymous hemianopsia	Hemioptic hypoplasia, R.E.	Exotropia, congenital nystagmus	Normal
7, 21, M	20/20	20/20	Complete right homonymous hemianopsia	Hemioptic hypoplasia, R.E.	Normal	Normal
8, 29, M	20/30	20/30	Incomplete right homonymous hemianopsia	Hemioptic hypoplasia, R.E.	Esotropia, congenital nystagmus	Cerebral palsy

glucose metabolism fell within the normal range in all four lobes of both hemispheres, including the right occipital lobes of these patients with left homonymous visual field loss. Peristriate cortex laterality index in one patient (Case 1) was increased significantly, which implied relatively decreased glucose uptake in Brodmann's regions 18 and 19 in the right hemisphere of this patient with a left homony-

mous field defect. Laterality index of the anterior calcarine cortex in the other patient (Case 2) was also significantly increased in a fashion appropriate for the mild damage on magnetic resonance imaging involving the right anterior occipital cortex.

In the patient in Case 1, posterior calcarine cortex laterality index without visual stimulation was 7.3%, which did not differ significant-

TABLE 2
RESULTS OF NEURO-IMAGING IN EIGHT PATIENTS

CASE NO.	STUDY		BRAIN AREA	RESULT
	COMPUTED TOMOGRAPHY	MAGNETIC RESONANCE IMAGING		
1	Yes	Yes	Visual Other	Damage to right optic radiations near occipital horn of lateral ventricle Slightly increased sulci
2	Yes	Yes	Visual Other	Dilated right occipital horn, damage to medial occipital and temporal lobes Normal
3	Yes	Yes	Visual Other	Absent right optic tract Normal
4	Yes	No	Visual Other	Damage extending from left occipital horn to anterior occipital lobe Slightly increased sulci
5	Yes	No	Visual Other	Damage extending from left occipital horn to anterior occipital lobe Slightly thickened bone of left occiput
6	Yes	No	Visual Other	Left occipital porencephaly Slight atrophy entire left cerebral hemisphere
7	Yes	No	Visual Other	Left temporal arachnoid cyst involving optic radiations Left temporal arachnoid cyst
8	Yes	No	Visual Other	Left occipital-porencephaly, right occipital-parietal watershed injury Increased sulci, atrophic right caudate

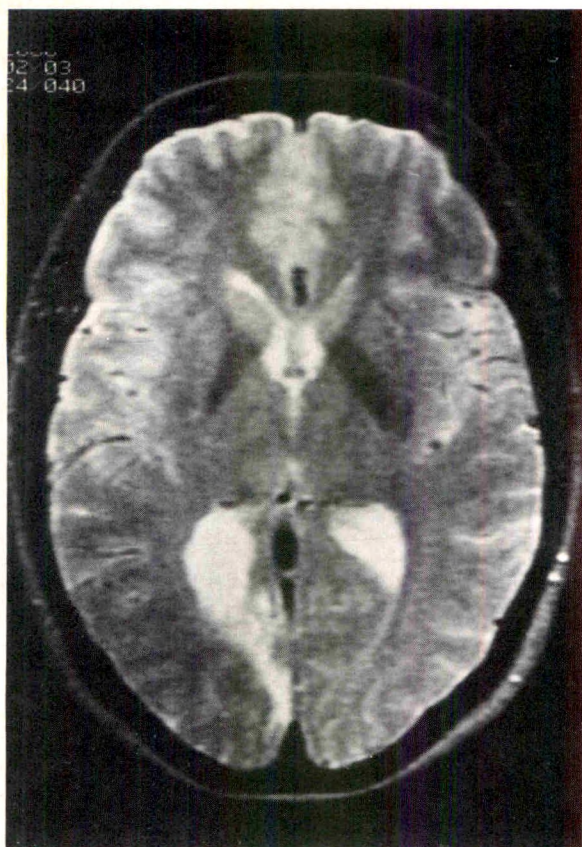


Fig. 1 (Bosley and associates) Case 2. T₂-weighted magnetic resonance image with an area of damage compatible with ischemia causing a bright signal involving the periventricular optic radiations, anterior occipital lobe, and posterior temporal lobe on the right. The patient's right is on the left of the figure.

ly from control subjects. The left posterior calcarine cortex was metabolically activated with whole field checkerboard visual stimulation, which increased the metabolic asymmetry to a laterality index of 14.0%.

Discussion

Congenital homonymous hemianopsia¹⁻⁵ may be an unnecessarily restrictive term because three of our patients had a history of birth trauma. Nevertheless, the term is well accepted to describe a clinical syndrome that can probably occur because of any damage to the retrochiasmal afferent visual system occurring in utero, at birth, or during the first several years of life. The incidence of optic atrophy, strabismus, and nystagmus in our patients is similar to



Fig. 2 (Bosley and associates). Case 3. T₁-weighted coronal magnetic resonance image showing hypoplastic right optic tract. The patient's right is on the left of the figure.

that in patients with congenital homonymous hemianopsia described by Bajandas, McBeath, and Smith.¹

Damage to primary visual cortex is clearly not essential to the syndrome because three patients from our series had damage only to the anterior calcarine cortex and another three patients had no identifiable calcarine cortex injury. Seven patients had lesions of the periventricular optic radiations, which made this the most common single area of the afferent visual system to be injured in congenital homonymous hemianopsia. Previous reports of congenital homonymous hemianopsia have stressed damage to cortex, including porencephaly^{15,16} and occipital dysplasia,^{2,17} but these lesions also included the distal optic radiations.

Lambert and associates¹⁸ observed that periventricular leukomalacia was universally present in children recovering from hypoxic cortical blindness. The periventricular region of immature brains is a vascular watershed area,¹⁹ whereas the parieto-occipital junction and parasagittal regions are more commonly damaged by hypoxic and ischemic injuries in adults.²⁰ Hypoxia and ischemia may be the most common mechanisms by which the afferent visual system of the immature brain is damaged, with periventricular optic radiations being the most vulnerable site. In this group of eight patients with visual field loss, other focal neurologic signs were present in only one patient, even though five patients had parenchymal abnormalities outside the afferent visual system on computed tomography.

Positron emission tomography was performed on two patients with normal computed

TABLE 3
CEREBRAL GLUCOSE METABOLISM WITH EYES
CLOSED

REGION	SIDE*	CASE 1	CASE 2	CONTROL SUBJECTS
Frontal lobe	R	4.62	5.28	4.67(0.80)
	L	4.54	5.22	4.76(0.86)
	LI	-1.75	-1.44	2.55(3.53)
Temporal lobe	R	3.16	4.74	3.95(0.67)
	L	2.96	4.70	4.02(0.76)
	LI	-6.54	-0.85	1.21(9.59)
Parietal lobe	R	3.43	4.53	3.84(0.60)
	L	3.80	4.54	3.98(0.56)
	LI	10.25	0.22	3.84(4.29)
Occipital lobe	R	3.43	4.52	3.98(0.60)
	L	3.55	4.62	3.96(0.57)
	LI	3.43	2.19	-0.39(2.60)
Anterior calcarine cortex	R	3.97	4.78	4.58(0.83)
	L	4.04	5.23	4.64(0.82)
	LI	1.74	8.99 [†]	1.58(4.83)
Posterior calcarine cortex	R	3.45	3.68	3.98(0.64)
	L	3.34	3.96	3.99(0.68)
	LI	-3.24	7.32	0.31(5.32)
Peristriate cortex	R	3.39	4.64	4.08(0.58)
	L	3.76	4.52	3.90(0.47)
	LI	10.34 [†]	-2.62	-4.23(7.50)
Lateral occipital cortex	R	3.59	4.63	3.74(0.55)
	L	3.69	4.59	3.77(0.53)
	LI	2.74	-0.87	0.70(2.90)
Whole brain		5.80	7.00	6.29(0.96)

*LI indicates laterality index.

[†]P < .05.

tomographic scans and largely intact occipital cortex by magnetic resonance imaging. Each patient had a total left homonymous hemianopsia, and the right occipital cortex had probably lacked visual stimulation since birth. Resting (eyes closed) cerebral glucose metabolism was normal throughout both brains with only subtle focal interhemispheric asymmetries in glucose uptake. Checkerboard stimulation to the whole visual field in one patient increased calcarine metabolic asymmetry as if only the right hemifield was receiving stimulation,²¹ which implied that the right visual cortex was not metabolically dependent on electrical activity in visual pathways of either the right or the left cerebral hemisphere.

Patients with homonymous hemianopsias caused by ischemic lesions of the optic radiations and occipital cortex acquired during adult life have severe abnormalities of glucose metabolism in the affected primary and association visual cortex.^{14,22,23} Chronically denervated, visually inactive occipital cortex in congenital homonymous hemianopsia seems to lack both

the normal metabolic activation of visual stimulation and the normal hypometabolism of adult denervation. This cortex may be less metabolically dependent than normal calcarine cortex on the character and quantity of ipsilateral afferent stimulation, or it may have acquired different afferent input after losing ipsilateral visual connections during development.

References

1. Bajandas, F. J., McBeath, J. B., and Smith, J. L.: Congenital homonymous hemianopsia. *Am. J. Ophthalmol.* 82:498, 1976.
2. Hoyt, W. F., Rios-Montenegro, E. N., Behrens, M. M., and Eckelhoff, R. J.: Homonymous hemioptic hypoplasia. Fundoscopic features in standard and red-free illustration in three patients with congenital hemiplegia. *Br. J. Ophthalmol.* 56:539, 1972.
3. Manor, R. S., and Korczyn, A. D.: Retinal red-free light photographs in two congenital conditions. A case of optic hypoplasia and a case of congenital hemianopsia. *Ophthalmologica* 173:119, 1976.
4. Tychen, L., and Hoyt, W. F.: Occipital lobe dysplasia. Magnetic resonance findings in two cases of isolated congenital hemianopsia. *J. Comput. Assist. Tomogr.* 2:539, 1978.
5. Maeda, S., Usuba, S., and Matsuyama, S.: Congenital homonymous hemianopsia. Three suspected cases. *Neuro-ophthalmol. Jpn.* 2:411, 1985.
6. Harbour, R., and El Gammal, T.: Congenital homonymous hemianopia and optic tract aplasia. *Ophthalmology* 95:173, 1988.
7. Ter-pogossian, M. M., Mullan, N. A., and Hood, J. T.: Design considerations for a positron emission tomograph (PETT V) for imaging of the brain. *J. Comput. Assist. Tomogr.* 2:539, 1978.
8. Phelps, M. E., Huang, S. C., Hoffman, E. J., Selin, C., Sokoloff, L., and Kuhl, D. E.: Tomographic measurement of local cerebral glucose metabolic rate in humans with F-18-fluoro-2-deoxy-D-glucose. Validation of method. *Ann. Neurol.* 6:371, 1979.
9. Reivich, M., Kuhl, D., Wolf, A., Greenberg, J., Phelps, M., Ido, T., Casella, V., Fowler, J., Hoffman, E., Alavi, A., Som, P., and Sokoloff, L.: The 18-F-fluorodeoxyglucose method for the measurement of local cerebral glucose utilization in man. *Circ. Res.* 44:127, 1979.
10. Kushner, M., Reivich, M., Alavi, A., Dann, R., and Burke, A.: Contralateral cerebellar hypometabolism following cerebral insult. A PET study. *Ann. Neurol.* 15:425, 1984.
11. Alavi, A., Dann, R., Chawluk, J., Alavi, J., Kushner, M., and Reivich, M.: Positron emission tomography imaging of regional cerebral glucose metabolism. *Semin. Nucl. Med.* 1:2, 1986.
12. Kushner, M., Schwartz, R., Alavi, A., Dann, R., Rosen, M., Silver, F., and Reivich, M.: Cerebral acti-

vation by non-meaningful monaural verbal auditory stimulation. *Brain Res.* 409:79, 1987.

13. Dann, R., Muehllehner, G., and Rosenquist, A.: Computer aided data analysis of ECT data. *J. Nucl. Med.* 24:82, 1983.

14. Bosley, T. M., Rosenquist, A. C., Kushner, M., Burke, A., Stein, A., Dann, R., Cobbs, W., Savino, P. J., Schatz, N. J., Alavi, A., and Reivich, M.: Ischemic lesions of the occipital cortex and optic radiations. Positron emission tomography. *Neurology* 35:470, 1985.

15. Lansche, R., Kearns, T. P., and Dodge, H. W.: Ophthalmologic aspects of porencephalic cysts. *Proc. Mayo Clin.* 33:664, 1958.

16. Trobe, J. D., Lorber, M. L., and Schlezinger, N. S.: Isolated homonymous hemianopia. *Arch. Ophthalmol.* 89:377, 1973.

17. Taylor, D. C., and Falconer, M. A.: Focal dysplasia of cerebral cortex in epilepsy. *J. Neurol. Neurosurg. Psychiatry* 34:369, 1971.

18. Lambert, S. R., Hoyt, C. S., Jan, J. E., Bar-kovich, J., and Flodmark, O.: Visual recovery from hypoxic cortical blindness during childhood. *Arch. Ophthalmol.* 105:1371, 1987.

19. DeReuck, J., Chatta, A. S., and Richardson, E. P.: Pathogenesis and evolution of periventricular leukomalacia in infancy. *Arch. Neurol.* 27:229, 1972.

20. Volpe, J. J.: Perinatal hypoxic-ischemic brain injury. *Pediatr. Clin. North Am.* 23:383, 1976.

21. Kushner, M. J., Rosenquist, A., Alavi, A., Rosen, M., Dann, R., Fazekas, F., Bosley, T. M., Greenberg, J., and Reivich, M.: Cerebral metabolism and patterned visual stimulation. Positron emission tomographic study of the human visual cortex. *Neurology* 38:89, 1988.

22. Kiyosawa, M., Mizuno, K., Hatazawa, J., Fukuda, H., Yamada, K., Ito, M., Matsuzawa, T., Watanuki, S., and Ido, T.: Metabolic imaging in hemianopsia using positron emission tomography with ¹⁸F-deoxyfluoroglucose. *Am. J. Ophthalmol.* 101:310, 1986.

23. Bosley, T. M., Dann, R., Silver, F. L., Alavi, A., Kushner, M., Chawluk, J. B., Savino, P. J., Sergott, R. C., Schatz, N. J., and Reivich, M.: Recovery of vision after ischemic lesions. Positron emission tomography. *Ann. Neurol.* 21:444, 1987.

OPHTHALMIC MINIATURE

"Sorry, m'dear," murmured her husband, though his lids half veiled his eyes like blinds drawn over his true feelings.

Dick Francis, *Longshot*
New York, G. P. Putnam, 1990, p. 76

Variable Expression of Albinism Within a Single Kindred

Susan Castronuovo, M.D., John W. Simon, M.D., Gillray L. Kandel, Ph.D.,
Albert Morier, O.D., Bruce Wolf, M.S., Carl J. Witkop, D.D.S.,
and Paul L. Jenkins, M.S.

We studied the albinotic characteristics in 13 members of a white family (age range, 2 to 73 years), which were graded according to severity and were correlated with visual acuity. Clinical, electrophysiologic, and biochemical characteristics of this family do not fit any known category of human albinism. The degree of heterogeneity in expression of albinotic features was unexpected. The correlation between visual acuity and nystagmus was particularly strong. The brown-haired propositus had severe skin involvement, iris transillumination, fundus hypopigmentation, and foveal hypoplasia. He had no manifest nystagmus, however, and his visual acuity was nearly normal. These observations suggest that nystagmus imposes a visual deficit beyond that related to foveal hypoplasia alone.

ALBINISM comprises a heterogeneous group of heritable disorders involving defective metabolism of the pigment melanin. In addition to variable hypopigmentation of the skin and hair, classic features include decreased visual acuity, nystagmus, photophobia, strabismus, severe astigmatism, iris transillumination, foveal hypoplasia, and hypopigmentation of the choroid

and retinal pigment epithelium.¹⁻³ Visual-evoked potential evidence of anomalous crossing at the optic chiasm of temporal retinal fibers has been demonstrated.⁴⁻⁶

In the current classification, tyrosinase-negative oculocutaneous albinism applies to individuals who have virtually no pigmentation of the skin, hair, or eyes.¹ In tyrosinase-positive oculocutaneous albinism, some melanin pigment is formed in the integument and in the ocular tissues. In ocular albinism the defect predominantly involves the eye, with only minor alterations in the skin and hair. Whereas oculocutaneous albinism is generally inherited as an autosomal recessive trait, ocular albinism has been described in both autosomal recessive and X-linked recessive forms.¹⁻³

We studied a family whose clinical, visual-evoked potential, biochemical, and genetic characteristics do not fit any known category of human albinism. Heterogeneity within this kindred permitted analysis of those features associated with poor visual acuity.

Patients and Methods

A 31-year-old man underwent a routine ophthalmic examination because of a family history of oculocutaneous albinism. The patient had typical white race features, with light brown hair, blue irides, and fair skin (Fig. 1). We examined the 13 members in three generations of his family, who ranged in age from 2 to 73 years. Full ophthalmic examination included cycloplegic refraction, assessment of best-corrected visual acuity, motility examination, and measurement of stereopsis (Randot). Iris transillumination, foveal hypoplasia, and fundus hypopigmentation were graded as previously described.⁷ These characteristics were designated as mild, moderate, marked, or severe. Iris and fundus photographs were obtained in co-operative patients and were used in grading. In

Accepted for publication Jan. 9, 1991.

From the Department of Ophthalmology, Albany Medical College, Albany, New York (Drs. Castronuovo, Simon, Kandel, and Morier, Mr. Wolf, and Mr. Jenkins); and Department of Oral Pathology and Genetics, University of Minnesota School of Dentistry, Minneapolis, Minnesota (Dr. Witkop). This study was supported in part by training grant EY0703702 and research grant EY05816 from the National Eye Institute to the Department of Ophthalmology, Albany Medical College; National Institutes of Health grant GM 22167-11 to the Department of Oral Pathology and Genetics, University of Minnesota; and an unrestricted grant from Research to Prevent Blindness, Inc.

Reprint requests to John W. Simon, M.D., Department of Ophthalmology, Albany Medical College, Albany, NY 12208.

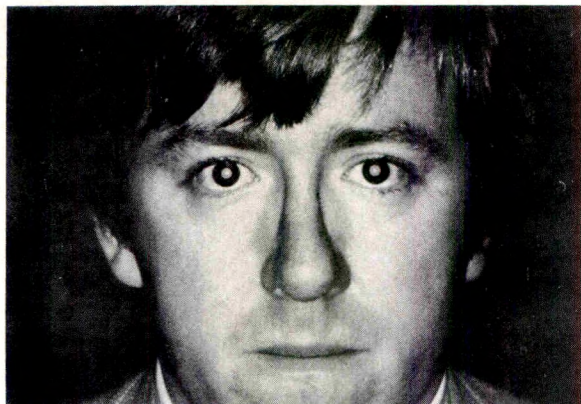


Fig. 1 (Castronuovo and associates). Propositus (Patient II-4) with mildly reduced visual acuity, moderate astigmatism, and fair complexion.

some cases, iris transillumination was absent. Nystagmus and strabismus were graded as absent, mild, moderate, marked, or severe. Nystagmus grades reflected both frequency and amplitude; strabismus grades reflected both angle and control. The following albinotic characteristics were graded as absent, mild, moderate, or severe: inability to tan, photophobia, and hypopigmentation of skin and hair.

Hair bulbs were tested qualitatively and quantitatively for tyrosinase activity after incubation in tyrosine and tyrosine plus cysteine. Assays used have been previously described; results were compared to a formalin-fixed control.⁸ Hair bulb hypopigmentation was graded as absent, mild, moderate, or severe. Electron microscopy of platelets (Patient II-6) was performed as previously described.⁹

Four-channel, bilateral, hemispheric visual-evoked potentials were recorded during binocular and monocular stimulation as described by Apkarian and associates.⁴ Asymmetry was graded from assessment of subtraction tracings of responses evoked by pattern-onset stimulation. These tracings were ranked independently by two of us (S.C. and G.L.K.) according to the degree of asymmetry. Ranks were 1 through 10, with 10 representing the most asymmetric recordings.¹⁰ Discrepancies were resolved by adding the ranks assigned each family member by the two judges. The resulting sum of ranks was then reordered. One three-way tie resulted.

Iris transillumination, foveal hypoplasia, fundus hypopigmentation, complexion, hair color, and nystagmus were judged by three of us (S.C., J.W.S., and A.M.). Discrepancies were

resolved by discussion, with reference to standard photographs.

Results

All graded characteristics except skin and hair hypopigmentation ranged from normal (mild or absent) to obviously albinotic (severe) (Fig. 2, Table 1). No cases of moderate iris transillumination, foveal hypoplasia or nystagmus, or of marked strabismus or nystagmus were identified. Patients II-4 and II-5 were fraternal twins who both resembled the father. All family members had blue irides.

Rankings (from 1 to 10) of the clinical, visual-evoked potential, and laboratory measurements of the family members for whom complete information was available (Patients I-1 and 2; II-1, 2, 3, 4, 6, and 7; and III-1 and 2) were established. Visual acuity (from best to worst) was ranked primarily by the better eye and secondarily by the worse eye. Stereopsis was ranked from 20 arc seconds to none. Grades of the remaining clinical characteristics determined their ranks, with mild or absent having the lowest ranks. In each case, higher ranks were assigned to the most albinotic characteristics.

The Spearman rank order correlations between visual acuity and albinotic characteristics were as follows: nystagmus, .89; poor stereopsis, .89; iris transillumination, .85; astigmatism, .76; visual-evoked potential asymmetry, .72; foveal hypoplasia, .72; skin hypopigmentation, .71; inability to tan, .60; fundus hypopigmentation, .56; photophobia, .52; strabismus, .49; and hair hypopigmentation, .20. The coefficients, which could range from 0 to 1, measure the strength of the relationship between visual acuity and each characteristic. For example, patients with the worst nystagmus and the poorest stereopsis had the worst visual acuity. By contrast, hair hypopigmentation was negligibly related to visual acuity.

These ranks were also used to contrast family members most and least affected with respect to each albinotic characteristic. To normalize each distribution of ranks, we subtracted 5.5 (the midpoint). This yielded positive numbers, which indicated that albinism was expressed, and negative numbers, which indicated that it was not expressed. For example, Patients II-1

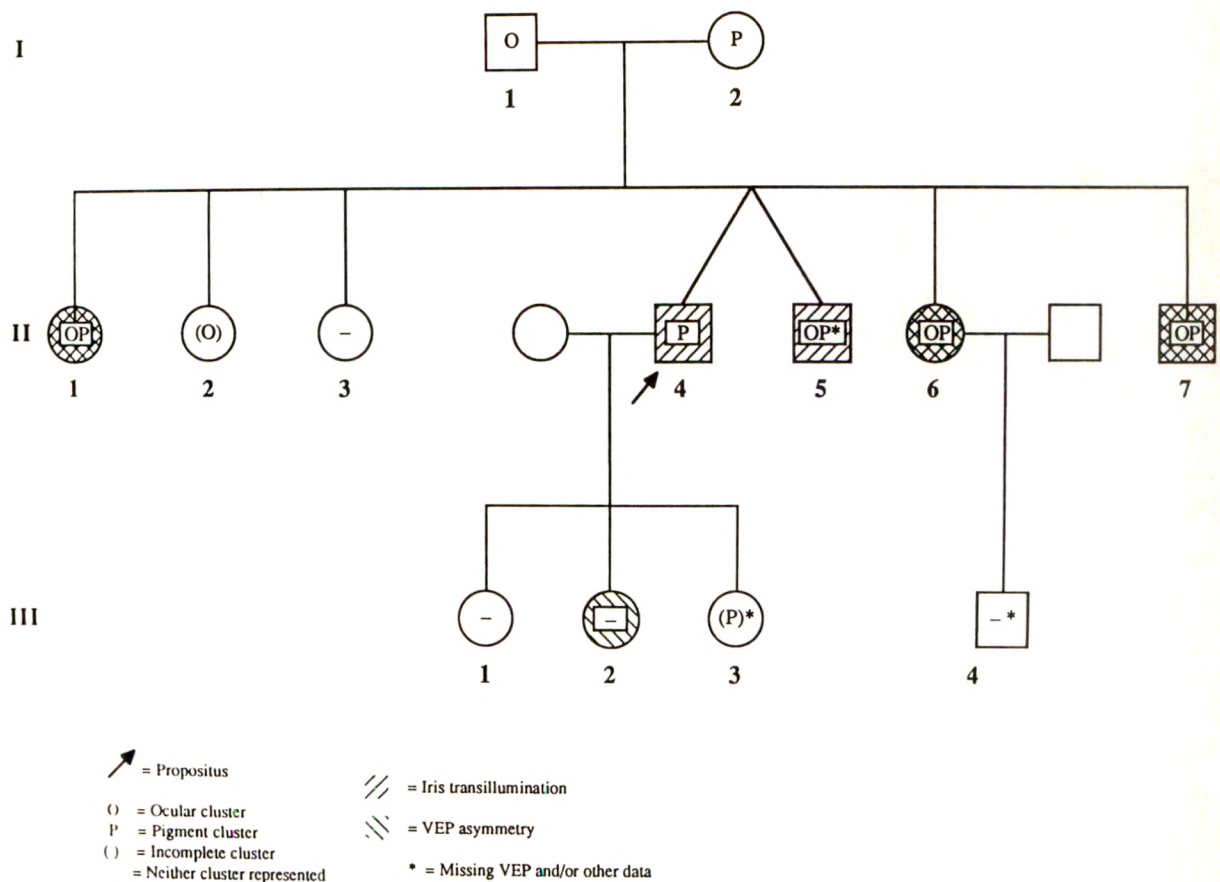


Fig. 2 (Castronuovo and associates). Pedigree of the family. (Arrow indicates propositus, and VEP indicates visual-evoked potential.)

and II-6 were positive for iris transillumination, whereas Patients I-2, II-2, II-3, and III-1 were negative for this trait.

By noting for each patient whether the score was positive or negative for each albinotic trait, we were able to identify two independent clusters (Table 2) of albinotic characteristics. Each cluster encompassed three traits: patients who expressed one tended also to be positive for the other two within the same cluster. Patients who did not express one trait tended also to be negative for the other two within the same cluster. The first group, which we designated the ocular cluster, included visual acuity, stereopsis, and nystagmus. Its concordance was significant ($P = .024$). The second group, which we designated the pigment cluster, included photophobia, tanning ability, and complexion. Its concordance was also significant ($P = .004$). Patients positive for one cluster were not necessarily positive for the other, and vice versa.

Patient I-1 was positive for the ocular cluster but negative for the pigment cluster, which was exactly opposite to Patient I-2.

Discussion

Patients II-1, II-5, II-6, and II-7 demonstrated the classic characteristics of albinism, including decreased visual acuity, nystagmus, foveal hypoplasia, and fundus hypopigmentation (Table 1). Except for Patient II-5, who was not tested, asymmetric monocular visual-evoked potentials of the albinotic type were demonstrated in these same patients.² Their skin and hair pigmentation, however, could not be distinguished from that of Patient I-2, who did not have any of the ocular features of albinism and was by all criteria unaffected.

If we were to examine the propositus (Patient

TABLE 1
GRADINGS OF CLINICAL FEATURES, RANKINGS OF VISUAL-EVOKED POTENTIAL ASYMMETRY, AND RESULTS OF LABORATORY ASSAYS

PATIENT NO., AGE (YRS)	VISUAL ACUITY IN EACH EYE	REFRACTION IN EACH EYE	STRABISMUS	STEREOPSIS (SECONDS OF ARC)	IRIS TRANSILLUMINATION	FOVEAL HYPOPLASIA	FUNDUS HYPOPIGMENTATION	NYSTAGMUS
I-1, 71	20/30+ 20/100	+5.00 +1.50 × 175 +5.50 +1.50 × 170	Moderate	None	Mild	Marked	Moderate	Mild
I-2, 62	20/20 20/20-	+3.00 +0.25 × 90 +3.50	Absent	20	Absent	Mild	Moderate	Absent
II-1, 40	20/80 20/60+	+1.25 +0.75 × 35 +1.00 +0.50 × 90	Absent	None	Severe	Marked	Severe	Severe
II-2, 39	20/40- 20/30	+0.50 +0.50 × 105 +2.25 +0.75 × 95	Absent	200	Absent	Mild	Moderate	Absent
II-3, 37	20/20 20/20	Plano Plano	Absent	20	Absent	Mild	Mild	Absent
II-4, 31	20/40+ 20/25-	Plano +3.50 × 95 -1.00 +3.25 × 90	Mild	200	Marked	Severe	Marked	Absent
II-5, 31	20/200 20/70	-4.50 +3.75 × 11 -2.00 +3.75 × 12	Severe	None	Severe	Severe	Marked	Severe
II-6, 27	20/70 20/80	Plano +1.50 × 100 +0.25 +3.25 × 65	Absent	None	Severe	Severe	Marked	Severe
II-7, 21	20/70 20/60	+6.25 +1.50 × 150 +6.25 +1.75 × 15	Severe	400	Marked	Marked	Marked	Severe
III-1, 13	20/20 20/20	-0.75 +0.50 × 115 -0.25 +0.25 × 75	Absent	20	Mild	Mild	Marked	Absent
III-2, 5	20/30 20/25	+0.50 +0.25 × 90 +0.75	Absent	30	Absent	Mild	Marked	Absent
III-3, 2	20/30 20/40	+2.25 +1.50 +0.50 × 75	Absent	—	Absent	Mild	Mild	Absent
III-4, 2	Central, steady, maintained Central, steady, maintained	+0.25 +1.25 × 115 +0.50 +0.50 × 90	Absent	—	Mild	Mild	Mild	Absent

II-4) as a single patient (Fig. 1), his mild reduction in corrected visual acuity, moderate astigmatism, blond fundi, and decreased macular reflex may not have suggested albinism. Despite his fair complexion, the patient looks unaffected: he has light brown hair and does not have manifest nystagmus. Albinism was suspected clinically only because of the family history and the finding of iris transillumination.

The findings in the proband are especially interesting in that his iris (Fig. 3) and fundus pigmentation is so characteristically albinotic and so similar to that of his affected siblings. Close inspection of his fovea showed as severe hypoplasia (Fig. 4) as in the most albinotic sibling (Figs. 5 and 6). Yet, in contrast to the visual acuities of his affected siblings, which were in the 20/60 to 20/70 range and characteristic of tyrosinase-positive albinism, his visual acuity of 20/25 was nearly normal.

This family does not fit any known category of albinism. This degree of variability within affected members of an albinotic family is unexpected. Phenotypic expression of an autosomal recessive disorder is dependent upon two recessive alleles, and individuals with homozygous expression generally show full expression of the condition.¹¹ Constitutive pigmentary differences are minimized within one family generation, and uniformity of phenotype is expected among siblings with homozygous expression.

A tyrosinase-positive form of albinism is clinically suggested by the pigmentation of the skin, hair, and irides of even the most affected family members. Their tanning ability and demonstrated hair bulb pigmentation further support this categorization. A unique feature of some affected family members was the marked increase in pigmentation on hair bulb incubation, despite extremely low levels of quantified

TABLE 1 (continued)
GRADINGS OF CLINICAL FEATURES, RANKINGS OF VISUAL-EVOKED POTENTIAL ASYMMETRY, AND RESULTS OF LABORATORY ASSAYS

PHOTO PHOBIA	HAIR HYPOPIG- MENTATION	INABILITY TO TAN	SKIN HYPOPIG- MENTATION	RANK ORDER OF VISUAL-EVOKED POTENTIAL ASYMMETRY	HAIR BULB HYPOPIGMENTATION			
					TYROSINASE ACTIVITY (PMOL/120 MIN)	CONTROL	TYROSINE INCUBATION	TYROSINE AND CYSTINE INCUBATION
Absent	Mild	Absent	Mild	3	0.000	Moderate	Absent	Absent
Mild	Moderate	Moderate	Moderate	5	0.369	—	—	—
Severe	Moderate	Moderate	Moderate	9	—	Severe	Absent	Absent
Absent	Mild	Mild	Mild	5	0.248	Moderate	Absent	Moderate
Absent	Mild	Absent	Mild	2	0.248	—	—	—
Mild	Moderate	Moderate	Moderate	5	0.000	Severe	Absent	Absent
Moderate	Moderate	Moderate	Moderate	—	—	—	—	—
Mild	Mild	Severe	Moderate	8	0.006	Severe	Absent	Absent
Mild	Mild	Moderate	Moderate	10	0.716	Severe	Absent	Absent
Absent	Mild	Absent	Mild	1	0.172	—	—	—
Absent	Mild	Absent	Mild	7	0.168	—	—	—
Absent	Moderate	Mild	Moderate	—	0.227	—	—	—
Absent	Mild	Mild	Mild	—	0.051	—	—	—

tyrosinase. For example, Patient II-6 had minute quantitative tyrosinase activity despite hair color that was even darker than that encountered in African tyrosinase-positive albinism (Table 1). It would appear that some genetic influence has inhibited pigmentation profoundly in the skin and eyes but much less in the hair. Similar variability in pigmentation has been noted in the Hermansky Pudlak syndrome.¹² The same patient, however, had normal numbers of platelet-dense bodies, which excluded this diagnosis.

Although the relatively dark hair color of Patients II-6 and II-7 might suggest autosomal recessive ocular albinism, the increase in their hair bulb pigmentation after incubation in tyrosine plus cysteine is inconsistent with this form. Yellow mutant albinism is unlikely because pheomelanin could not be demonstrated. The defect in this family most closely resembled

minimal pigment albinism, proposed by King and associates¹³ and Jay, Witkop, and King¹⁴ to represent compound albinism with different alleles at the tyrosinase locus. None of their patients, however, developed the degree of hair and skin pigmentation seen in the patients of our study. It is conceivable that the two clusters identified in our family, which were reciprocally expressed in Patients I-1 and I-2, may reflect two separate interacting gene loci.

Clusters of albinotic characteristics (Table 2) suggest that two different but allelic genes may be present in this family. The mutant gene in the presumed heterozygous father (+, a1) is expressed as decreased visual acuity, decreased stereopsis, and nystagmus. The mutant gene in the presumed heterozygous mother (+, a2) is expressed as photophobia, inability to tan, and hypopigmentation. If this were so, Patients II-2 and II-3, who are not albinotic, would have

TABLE 2
CLUSTERS OF ALBINOTIC CHARACTERISTICS*

PATIENT NO.	OCULAR CLUSTER			PIGMENT CLUSTER		
	VISUAL ACUITY	STEREOPSIS	NYSTAGMUS	PHOTOPHOBIA	INABILITY TO TAN	SKIN HYPOPIGMENTATION
I-1	Yes	Yes	Yes	No	No	No
I-2	No	No	No	Yes	Yes	Yes
II-1	Yes	Yes	Yes	Yes	Yes	Yes
II-2	Yes	Yes	No	No	No	No
II-3	No	No	No	No	No	No
II-4	No	No	No	Yes	Yes	Yes
II-6	Yes	Yes	Yes	Yes	Yes	Yes
II-7	Yes	Yes	Yes	Yes	Yes	Yes
III-1	No	No	No	No	No	No
III-2	No	No	No	No	No	No

*Yes indicates expression of the albinotic characteristic, and no indicates nonexpression of the albinotic characteristic.

received a normal wild-type gene from each parent (+, +). Albinotic Patients II-1, II-6, and II-7 would have received a mutant gene from each parent (a1, a2). Patient II-4 would be heterozygous, having received a normal gene from the father and a mutant gene from the mother (+, a2).

The quantitative hair bulb tyrosinase assay measures easily extractable, soluble enzyme unbound to the melanosome matrix. The quantitative tyrosinase activity in hair bulbs of obligate heterozygotes for tyrosinase-negative albinism have zero or near zero activity rather than approximately half of the activity expected in a heterozygote for an enzymatic disorder. It is believed that in the tyrosinase-negative heterozygote the half-normal dose of enzyme is immediately bound to the melanosome matrix, leaving no soluble unbound tyrosinase that the

assay method detects. Evidence that albinotic Patients II-2 and II-4 and presumed heterozygous Patient II-5 have melanosome-bound tyrosinase, despite no activity of assayed free tyrosinase, is the definite pigment present in the hair and the increase in pigmentation of hair bulbs after incubation in tyrosine substrate.

The biochemical inconsistency of two allelic genes as an explanation for the observations in this family is the high free-tyrosinase activity in the hair bulbs of Patient II-7. High free-tyrosinase activity might result if for some reason there were a defect in melanosome formation or in enzyme binding to the melano-

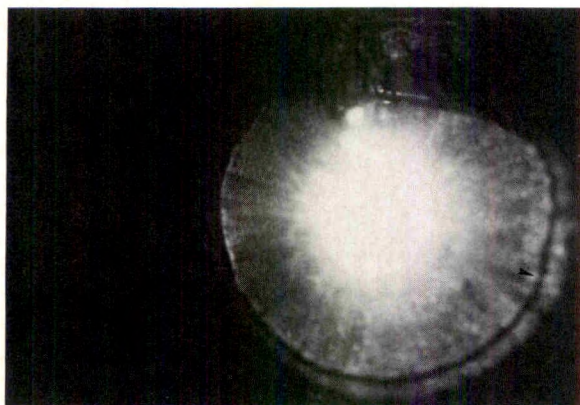


Fig. 3 (Castronuovo and associates). Marked iris transillumination in the proband (Patient II-4). (Arrow indicates lens equator.)

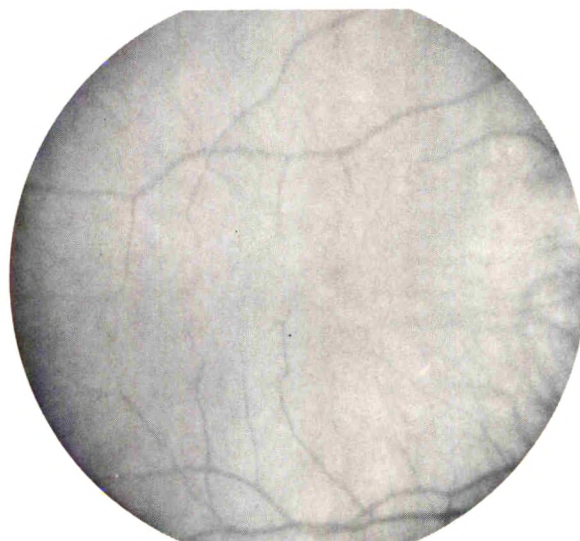


Fig. 4 (Castronuovo and associates). Marked fundus hypopigmentation and severe foveal hypoplasia in the proband (Patient II-4).



Fig. 5 (Castronuovo and associates). Moderate complexion and mild hair hypopigmentation (light brown) in Patient II-6.

some matrix in this patient. Ultrastructural studies might elucidate this possibility. The present evidence, however, suggests that an unidentified factor is present in the pathogenesis of the pigment defect in this family.

The cause of the visual impairment in albinism is uncertain. Perhaps the most obvious possibility is the characteristic foveal hypoplasia. As demonstrated by Fulton, Albert, and Craft,¹⁵ none of the clinical or histologic features of the normal fovea can be identified in albinotic eyes. Wilson and associates^{16,17} suggested that increased photoreceptor spacing is the basis for poor visual acuity in albinism. Surprisingly, foveal hypoplasia did not appear in the cluster with visual acuity. The findings in our propositus, who had visual acuity of 20/25 despite clinically severe foveal hypoplasia (Fig. 4), also failed to link visual acuity and foveal hypoplasia. His foveas were more hypoplastic than those of Patient II-1, whose visual acuity was substantially worse. Light scattering and damage from free radicals impinging upon the unprotected retina have been suggested as a second possible cause of the visual deficit.¹⁸ However, neither iris transillumination nor fundus hypopigmentation appeared in the cluster with visual acuity. The propositus, with nearly normal visual acuity, nevertheless had marked hypopigmentation of both iris and fundus.

Previous reports have tended to correlate the severity of albinotic characteristics with the degree of visual impairment: less pigmented individuals generally have worse visual function.^{1,2} We analyzed each of the clinical features of albinism in an attempt to determine, for this family, which are more strongly related to the visual acuity deficit. The strongest correlations

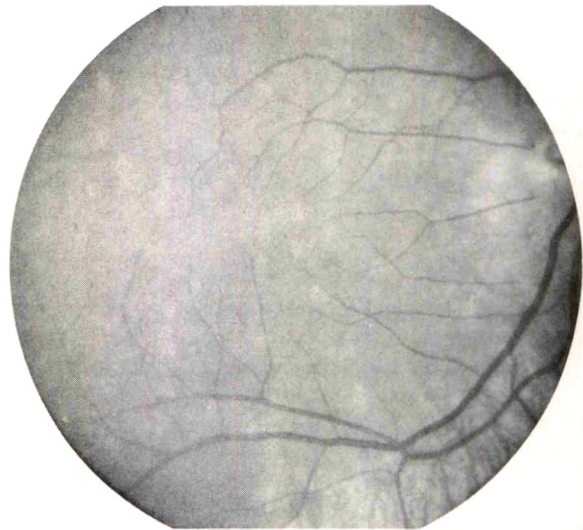


Fig. 6 (Castronuovo and associates). Marked fundus hypopigmentation and severe foveal hypoplasia in Patient II-6.

with visual acuity deficit ($P < .01$) were seen for nystagmus, stereopsis, and iris transillumination. The correlation between nystagmus and visual acuity was particularly strong. The importance of nystagmus was evident in the propositus, with severe foveal hypoplasia, no nystagmus, and good vision. His clinical findings contrast with those of Patient II-1, who had milder foveal hypoplasia, severe nystagmus, and substantially poorer vision. These observations suggest that nystagmus imposes a visual deficit beyond that related to foveal hypoplasia alone.

Our analyses demonstrate that albinism can be variably expressed, even within a single family. Such variability has been noted in albinism associated with Prader-Willi syndrome.¹⁹ Patients with albinism need not have nystagmus and are likely to have better visual acuity if they do not. Some of the features typically encountered in albinism, such as foveal hypoplasia and iris transillumination, need not be associated with major visual acuity impairment. We believe further studies of families with albinism will help elucidate the genetic and structural basis for the visual impairment.

References

1. Witkop, C. J., Quevedo, W. C., and Fitzpatrick, T. B.: Albinism and other disorders of pigment metabolism. In Stanbury, J. B., Wyngaarden, J. B., and

Fredrickson, D. S. (eds.): *The Metabolic Basis of Inherited Disease*, ed. 5. New York, McGraw-Hill, 1983, pp. 301-346.

2. Kinnear, P. E., Jay, B., and Witkop, C. J.: Albinism. *Surv. Ophthalmol.* 30:75, 1985.

3. O'Donnell, F. E., and Green, R. W.: The eye in albinism. In Duane, T. D., and Jaeger, E. A. (eds.): *Clinical Ophthalmology*, vol. 4, ed. 2, chap. 38. Philadelphia, Harper and Row, 1985, pp. 1-23.

4. Apkarian, P., Reits, D. Spekrijse, H., and van Dorp, D.: A decisive electrophysiologic test for human albinism. *Electroencephalogr. Clin. Neurophysiol.* 55:513, 1983.

5. Guillery, R. W., Okoro, A. N., and Witkop, C. J.: Abnormal visual pathways in the brain of a human albino. *Brain Res.* 96:373, 1975.

6. Creel, D., Spekrijse, H., and Reits, D.: Evoked potentials in albinos. Efficacy of pattern stimuli in detecting misrouted optic fibers. *Electroencephalogr. Clin. Neurophysiol.* 52:595, 1981.

7. Simon, J. W., Kandel, G. L., Krohel, G. B., and Nelsen, P. T.: Albinotic characteristics in congenital nystagmus. *Am. J. Ophthalmol.* 97:320, 1984.

8. King, R. A., and Witkop, C. J.: Hairbulb tyrosinase activity in oculocutaneous albinism. *Nature* 263:69, 1976.

9. White, J. G., Edson, J. R., Desnick, S. J., and Witkop, C. J., Jr.: Studies of platelets in a variant of the Hermansky-Pudlak syndrome. *Am. J. Pathol.* 63:319, 1971.

10. Kandel, G. L., Castronuovo, S., Simon, J. W., Wolf, B. M., and Morier, A. M.: Correlation of VEP asymmetry with albinotic features in a family with

oculocutaneous albinism. *ARVO abstracts. Supplement to Invest. Ophthalmol. Vis. Sci.* Philadelphia, J. B. Lippincott, 1988, p. 432.

11. Vogel, F., and Motulsky, A. G.: *Human Genetics*, ed. 2. Heidelberg, Springer-Verlag, 1986, p. 116.

12. Summers, C. G., Knoblock, W. H., Witkop, C. J., and King, R. A.: Hermansky Pudlak syndrome. Ophthalmologic findings. *Ophthalmology* 95:545, 1988.

13. King, R. A., Wirtschafter, J. D., Olds, D. P., and Burmbaugh, J.: Minimal pigment. A new type of oculocutaneous albinism. *Clin. Genet.* 29:42, 1986.

14. Jay, B., Witkop, C. J., and King, R. A.: Albinism in England. *Birth Defects* 18:319, 1982.

15. Fulton, A. B., Albert, D. M., and Craft, J. L.: Human albinism. Light and electron microscopy study. *Arch. Ophthalmol.* 96:305, 1978.

16. Wilson, H. R., Mets, M. B. Nagy, S., and Kresel, A. B.: Albino spatial vision as an instance of arrested visual development. *Vision Res.* 28:979, 1988.

17. Wilson, H. R., Mets, M. B. Nagy, S. E., and Ferrara, V. P.: Spatial frequency and orientation tuning of spatial visual mechanisms in human albinos. *Vision Res.* 28:991, 1988.

18. Feeney, L., and Berman, E. R.: Oxygen toxicity. Membrane damage by free radicals. *Invest. Ophthalmol.* 15:789, 1976.

19. Creel, D. J., Bendel, C. M., Wiesner, G. L., Wirtschafter, J. D., Arthur, D. C., and King, R. A.: Abnormalities of the central visual pathways in Prader-Willi syndrome associated with hypopigmentation. *N. Engl. J. Med.* 314:1606, 1986.

Loss of Contrast Sensitivity in Cystic Fibrosis

Lawrence E. Leguire, Ph.D., Karl S. Pappa, M.D., Mary Lou Kachmer, M.D.,
Gary L. Rogers, M.D., and Don L. Bremer, M.D.

We measured the contrast sensitivity function in a 16-year-old boy with cystic fibrosis, before and during vitamin A supplementation. Before vitamin A supplementation, serum levels of vitamin A were abnormally low, the electroretinogram was reduced, and contrast sensitivity was abnormally low at all spatial frequencies. During vitamin A supplementation (25,000 IU/day), serum levels of vitamin A became low normal, the electroretinogram returned to normal, and the overall contrast sensitivity function improved by 94%. We propose that the contrast sensitivity function may be abnormal in patients with cystic fibrosis who have reduced retinal function secondary to vitamin A deficiency.

SPAIDE AND ASSOCIATES¹ reported that in patients with cystic fibrosis the contrast sensitivity function showed an overall loss compared to normal control subjects. The overall loss of the contrast sensitivity function was evident even in patients with cystic fibrosis with normal visual acuity and without chloramphenicol treatment. Given that few of the patients with cystic fibrosis had retinal abnormalities, Spaide and associates¹ proposed that the overall loss of contrast sensitivity function may be attributed to subclinical optic nerve dysfunction.

Lindenmuth, Del Monte, and Marino² noted that more than 85% of patients with cystic fibrosis have the potential for a vitamin A deficiency. It is well established that vitamin A is essential for photoreceptor function.³ A deficiency in vitamin A can cause retinal changes that are not typically noted on ophthalmic examination.⁴

We examined a patient with cystic fibrosis who also had a vitamin A deficiency. We measured the contrast sensitivity function before vitamin A supplementation and found an abnormal contrast sensitivity function similar to that reported by Spaide and associates.¹ During vitamin A supplementation, however, the contrast sensitivity function improved significantly. These results suggest the possibility that contrast sensitivity function losses in patients with cystic fibrosis can be caused by subclinical retinal abnormalities secondary to vitamin A deficiency.

Case Report

A 16-year-old boy with cystic fibrosis since birth was referred to our institution for night blindness. Medical history included multiple colectomies for meconium ileus and development of diabetes at the age of 8 years. Medications included pancrelipase, albuterol, and insulin. The patient was also taking multiple vitamins, and compliance was reported to be good based on an interview with the patient's mother. The patient had a five-year history of recurrent episodes of a red, blotchy rash resembling hives, accompanied by severe joint pain and swelling, chills, malaise, fatigue, and fever.

Ophthalmic examination disclosed visual acuity of 20/30 in both eyes and multiple Bitot's spots on the conjunctiva of each eye. Visual fields and color vision were normal. Results of examination, with pupils dilated, of the retinas and optic nerves were unremarkable. Electroretinography, under light and dark adaptation conditions, showed reduced b-wave amplitude responses from both eyes. Serum levels of vitamin A were found to be abnormally low (less than 10 µg/dl; normal, 30 to 95 µg/dl).

Monocular contrast sensitivity functions were measured with a wall-mounted, contrast sensitivity function chart that consisted of eight contrast levels at five spatial frequen-

Accepted for publication Jan. 3, 1991.

From the Department of Ophthalmology, Columbus Children's Hospital, Columbus, Ohio. This study was supported in part by the Ohio Lion's Eye Research Foundation.

Reprint requests to Lawrence E. Leguire, Ph.D., Department of Ophthalmology, Columbus Children's Hospital, 700 Children's Dr., Columbus, OH 43205.

cies.^{5,6} A three-alternative, forced-choice procedure was used to measure the contrast sensitivity function as previously described.⁷ Contrast sensitivity functions were measured twice in the patient: before and four months after the start of vitamin A supplementation (25,000 IU/day). With vitamin A supplementation, serum levels of vitamin A were low normal (40 $\mu\text{g/dl}$), and electroretinograms returned to normal amplitudes.

Results

The Figure shows contrast sensitivity functions, averaged between the right and left eyes, before and during vitamin A supplementation

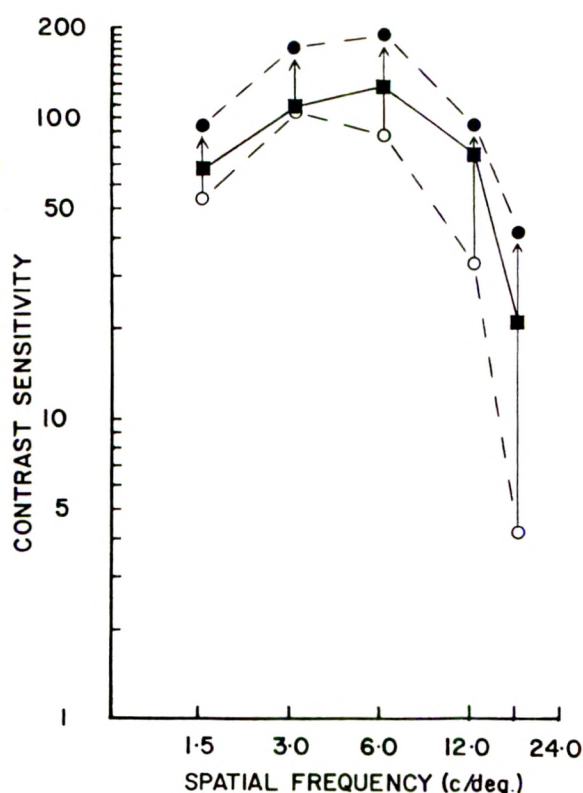


Figure (Leguire and associates). Contrast sensitivity functions are shown for a patient with cystic fibrosis before (open circles and dashed line) and during (closed circles and dashed line) vitamin A supplementation. The arrows at each spatial frequency illustrate the overall 94% improvement in the contrast sensitivity function with vitamin A supplementation. The normal contrast sensitivity function (closed squares and solid line) represents the mean of 15 normal adults.

and the mean contrast sensitivity function of 15 normal adults. Before vitamin A supplementation the contrast sensitivity function was below normal at all spatial frequencies. With vitamin A supplementation the overall contrast sensitivity function improved by 94%. Assuming independence of spatial frequencies, the overall increase in contrast sensitivity function was statistically significant (paired t -test = 4.16, $df = 4$, $P < .02$). The increase in contrast sensitivity function cannot be attributed to a learning effect, aging, or other extraneous variables.⁷

Discussion

The contrast sensitivity function, averaged between the right and left eyes, found in a patient with cystic fibrosis with a vitamin A deficiency was similar to that found in a group of patients with cystic fibrosis described by Spaide and associates.¹ The overall contrast sensitivity function was found to be decreased relative to that of a normal control group. We estimated the overall decrease in contrast sensitivity in patients with cystic fibrosis compared to the control group, as reported by Spaide and associates,¹ to be approximately 52%. This estimate agrees with the overall decrease in contrast sensitivity before vitamin A supplementation in our patient of 48%. Our results suggest the possibility that the results found by Spaide and associates¹ may have been caused by subtle losses of retinal-photoreceptor function associated with vitamin A deficiency. Approximately 85% of patients with cystic fibrosis have the proclivity for vitamin A deficiency.² Additionally, the electroretinogram results indicate that the vitamin A deficiency caused a functional retinal abnormality.

It could be argued that the patients with cystic fibrosis studied by Spaide and associates¹ did not have a subclinical vitamin A deficiency because 31 of their 32 (97%) patients with cystic fibrosis were taking vitamin supplements. Our patient, however, was also taking vitamin supplements. As noted by Sommer,⁸ 5,000 to 10,000 IU (which is the typical amount of vitamin A in multivitamins) may not be enough to maintain liver storage of vitamin A in patients with cystic fibrosis. Sommer⁸ suggested that 25,000 to 50,000 IU may be required to maintain liver storage of vitamin A in patients with cystic fibrosis. This important point is illustrated by the findings in our patient, in that

his condition was maintained on 25,000 IU/day of vitamin A; yet, his serum levels were only low normal.

These results in combination with the results of Spaide and associates¹ suggest the possibility that the contrast sensitivity function may be valuable in the detection of subtle losses of retinal function in patients with cystic fibrosis. The photoreceptors are the most sensitive organ to manifest signs of vitamin A deficiency.⁹ Given that vitamin A deficiency may exist even with normal vitamin A serum levels,¹⁰ the contrast sensitivity function may be valuable in the detection and evaluation of retinal dysfunction secondary to a vitamin A deficiency in patients with cystic fibrosis.

References

1. Spaide, R. F., Diamond, G., D'Amico, R. A., Gaerlan, P. F., and Bisberg, D. S.: Ocular findings in cystic fibrosis. *Am. J. Ophthalmol.* 103:204, 1987.
2. Lindenmuth, K. A., Del Monte, M., and Marino, L. R.: Advanced xerophthalmia as a presenting sign in cystic fibrosis. *Ann. Ophthalmol.* 21:189, 1989.
3. Sommer, A.: Effects of vitamin A deficiency on the ocular surface. *Ophthalmology* 90:592, 1983.
4. Partamian, L. G., Sidrys, L. A., and Tripathi, R. C.: Iatrogenic night blindness and keratoconjunctival xerosis. *N. Engl. J. Med.* 301:944, 1979.
5. Ginsburg, A. P.: A new contrast sensitivity vision test chart. *Am. J. Optom. Physiol. Opt.* 61:403, 1984.
6. Leguire, L. E., Rogers, G. L., and Bremer, D. L.: Functional amblyopia in a single continuum of visual impairment on contrast sensitivity function. *Binoc. Vision* 2:199, 1987.
7. ———: Amblyopia. The normal eye is not normal. *J. Pediatr. Ophthalmol. Strabismus* 27:31, 1990.
8. Sommer, A.: Vitamin A deficiency today. Conjunctival xerosis in cystic fibrosis. *J. R. Soc. Med.* 82:1, 1989.
9. McLaren, D. S.: *Malnutrition and the Eye*. New York, Academic Press, 1963, pp. 162–229.
10. Wechsler, H. L.: Vitamin A deficiency following small-bowel bypass surgery for obesity. *Arch. Dermatol.* 115:73, 1979.

Scleritis and Wegener's Granulomatosis in Children

Robert D. Sacks, M.D., E. Lee Stock, M.D., Susan E. Crawford, M.D.,
Mark J. Greenwald, M.D., and Richard B. O'Grady, M.D.

We treated two children with scleritis (one unilateral, one bilateral), in whom Wegener's granulomatosis was diagnosed on the basis of pathologic changes in respiratory tract mucosa. Both patients were girls, 13 and 14 years of age, respectively. One patient had otitis media and a nodular scleritis. Laboratory test results demonstrated an increased erythrocyte sedimentation rate and microscopic hematuria. A biopsy of the sinus confirmed the diagnosis of Wegener's granulomatosis. The second patient had fever, arthralgias, a nonproductive cough, and bilateral scleritis. Laboratory test results demonstrated an increased erythrocyte sedimentation rate, positive test results for rheumatoid factor, and bilateral pulmonary nodules on chest x-ray. Open-lung biopsy confirmed the diagnosis of Wegener's granulomatosis. Both patients responded well to treatment with a combination of prednisone and cyclophosphamide.

SCLERITIS occurs rarely in children. A few pediatric cases have previously been reported,^{1,3} for which no definitive etiologic origin was established.

Wegener's granulomatosis is a multisystem disease, primarily of adults, which consists of upper and lower respiratory tract necrotizing granulomas and vasculitis, varied degrees of generalized small vessel vasculitis, and a focal necrotizing glomerulonephritis. A limited form of the disease without renal involvement has a

better prognosis.⁴ We treated two children in whom scleritis was the initial manifestation of Wegener's granulomatosis.

Case Reports

Case 1

A 13-year-old girl entered the hospital for treatment of otitis and scleritis. The patient had recurrent otitis media treated with bilateral myringotomy one year before admission. Five weeks earlier, she had developed arthralgias, decreased appetite with mild weight loss, and fatigability. Recurrent otitis media one week later necessitated insertion of an ear tube and treatment with oral cefaclor antibiotic. Ten days before admission, the patient developed a white spot on the right cornea, which was diagnosed as bacterial keratitis by an ophthalmologist and treated with topical tobramycin eyedrops. The condition almost resolved after four days, but then the right eye became red and painful. The ophthalmologist then prescribed gentamicin sulfate eyedrops, bacitracin ophthalmic ointment, and oral penicillin. Four days before admission, the pain increased, and photophobia and blurred vision developed. The patient was admitted to Children's Memorial Hospital for fever and lethargy in addition to the ocular complaints.

Initial findings included visual acuity of R.E.: 20/30 and L.E.: 20/20. Results of examination of the pupils were normal, and ocular movements were full. There was mild right upper eyelid blepharoptosis with edema. Slit-lamp examination demonstrated conjunctival injection superiorly with prominent scleral vessels and scleral edema. A 3 × 4-mm scleral nodule was noted superiorly with adjacent small, discrete, limbal infiltrates. There was no associated corneal thinning. The anterior chamber was clear, and intraocular pressure and results of a fundus examination were normal.

The girl appeared chronically ill. Yellow-white discharge drained from the right eye, and

Accepted for publication Dec. 28, 1990.

From the Department of Ophthalmology, Northwestern University Medical School, and Lakeside Veteran's Administration, Chicago, Illinois (Drs. Sacks, Stock, and O'Grady); and Department of Pathology (Dr. Crawford) and Division of Ophthalmology (Dr. Greenwald), Children's Memorial Hospital, Chicago, Illinois. This study was supported in part by an unrestricted grant from Research to Prevent Blindness, Inc.

Reprint requests to E. Lee Stock, M.D., 303 E. Chicago Ave., Department of Ophthalmology, Northwestern University Medical School, Chicago, IL 60611.

the tympanic membrane was inflamed. Bilateral ear tubes were in place. Results of the remainder of the physical examination were normal.

Initial laboratory testing included normal results of a complete blood cell count, electrolyte level, and creatinine level. Urinalysis demonstrated microscopic hematuria (four to five red blood cells per high-power field). Westergren erythrocyte sedimentation rate was 41 mm/hour (normal, 0 to 20 mm/hour). Rheumatoid factor, antinuclear antibody, and complement levels were normal. Results of a chest x-ray were normal. Computed tomography disclosed probable right mastoiditis.

Initial treatment consisted of intravenous gentamicin sulfate and topical 1% ocular prednisolone acetate, which produced minimal improvement in both the ocular condition and otalgia after 48 hours. Results of a culture of the cornea were negative, but culture of fluid draining from the right ear grew *Achromobacter xylosoxidans*. The regimen was changed to oral trimethoprim/sulfamethoxazole and prednisone, which resulted in ocular and systemic improvement within 36 hours.

Based on clinical findings, biopsy specimens of the middle ear, maxillary sinus mucosa, subglottic mucosa, and bone from the maxillary sinus were obtained. Only the maxillary mucosa was abnormal. There was marked vasculitis with polymorphonuclear and plasma cell infiltration in the vessel walls as well as occasional granuloma and multinucleated giant cells (Fig. 1). The histopathologic diagnosis was Wegener's granulomatosis. Bacterial and fungal cultures of biopsy tissue were negative.

After a ten-day regimen of systemic prednisone, both the scleritis and systemic symptoms had greatly improved, and the patient was discharged from the hospital. Increased microscopic hematuria, proteinuria, serum creatinine level, and blood urea nitrogen level developed four weeks later. Cyclophosphamide was added to the treatment regimen. For a short time, azotemia continued to progress, and hyperkalemia developed, which required peritoneal dialysis. During the ensuing two months, renal function showed marked improvement. The scleritis resolved completely with cyclophosphamide and corticosteroid therapy.

Case 2

A 14-year-old girl entered the hospital with fever, arthralgias, nasal congestion with a mild nonproductive cough, decreased appetite, and fatigue of three weeks' duration. Two days be-

fore admission the patient had developed irritation, tearing, redness, and dull pain in both eyes.

Ocular examination disclosed visual acuity of 20/20 in both eyes as well as normal pupils and ocular motility. Slit-lamp examination demonstrated mild conjunctival injection and moderate bilateral scleral injection and edema superiorly in both eyes. Both anterior chambers were deep and clear, and intraocular pressure and results of fundus examination were normal.

Laboratory results included a Westergren erythrocyte sedimentation rate of 37 mm/hour, a positive rheumatoid factor test at 1:1,280 dilution, negative antinuclear antibody test, and normal complement levels. Urinalysis demonstrated four to eight red blood cells per high-power field. A chest x-ray disclosed multiple bilateral pulmonary nodules. A tuberculin skin test was negative.

The patient underwent an open-lung biopsy, which confirmed a microscopic diagnosis of Wegener's granulomatosis (Fig. 2). There was evidence of marked vasculitis with destruction of the vessel walls. Many inflammatory cells consisting of both polymorphonuclear leukocytes and lymphocytes with a moderate amount of giant cells were also noted. Bacterial and fungal cultures of the biopsy specimen were negative. Treatment with oral prednisone and cyclophosphamide was initiated, with resolution of systemic symptoms and scleritis after seven days.

Discussion

Wegener's granulomatosis is a disease mainly of adults, with the average age of onset in the fourth to fifth decades of life and relatively rare occurrence in patients younger than the age of 16 years. The recorded frequency of ocular involvement in Wegener's granulomatosis has ranged from 29% to 48%.⁵⁻⁷ The anterior segment is commonly the site of focal ocular involvement, with the sclera and episclera involved in up to 38% of cases.⁷ Contiguous involvement of the orbit is also commonly noted.^{5,7} Scleritis associated with Wegener's granulomatosis can be devastating, with subsequent blindness despite aggressive therapy.⁸⁻¹⁰

In 1985, Parelhoff, Chavis, and Friendly¹¹ reviewed the literature and found only 21 well-documented cases of Wegener's granulomatosis in children under 16 years of age, of whom

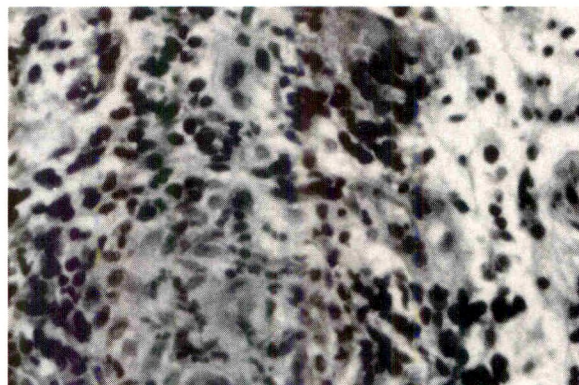
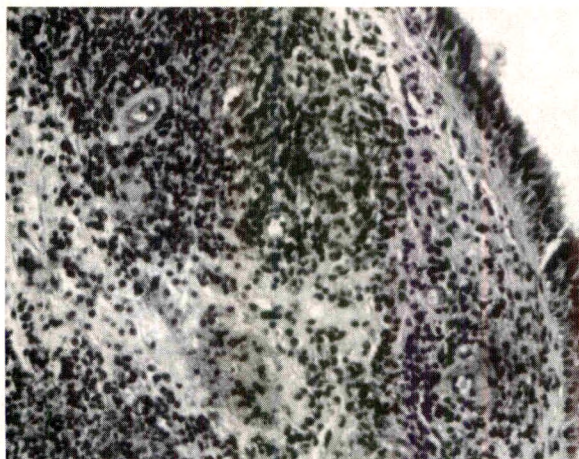


Fig. 1 (Sacks and associates). Case 1. Maxillary mucosa biopsy specimen. Left, Subepithelial zone is thickened by perivascular chronic inflammatory cell infiltrate and an area of necrosis (hematoxylin and eosin, $\times 100$). Right, Chronic inflammatory cells surround a central histiocytic focus containing a multinucleated giant cell (hematoxylin and eosin, $\times 450$).

eight had ocular or orbital signs, but none had scleritis. A subsequent report described four children under age 14 years with Wegener's granulomatosis; two had conjunctivitis as the only ocular manifestation.¹² In 1986, Halstead, Karmody, and Wolff¹³ described 50 patients with Wegener's granulomatosis, including four patients younger than 16 years of age. One of their patients had a corneal ulcer as the initial symptom. Mohanlal and associates¹⁴ described an 11-year-old girl with Wegener's granulomatosis but without ocular involvement. In contrast to previous reports, both of our patients

had scleritis as one of the initial manifestations of the underlying systemic process.

The average age of onset of scleritis at one referral center was 46.6 years.¹⁵ Watson and Hayreh¹⁶ reported a peak incidence in the fourth decade in men and two peaks in women: one in the third decade and one in the sixth decade.

Scleritis is the result of granulomatous changes of the sclera believed to be an immune response either within the scleral tissue or its vascular supply.^{17,18} Because scleritis is usually secondary to a systemic disease and the inflam-

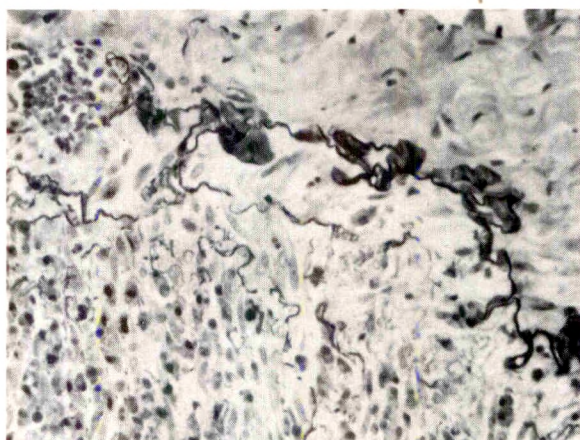
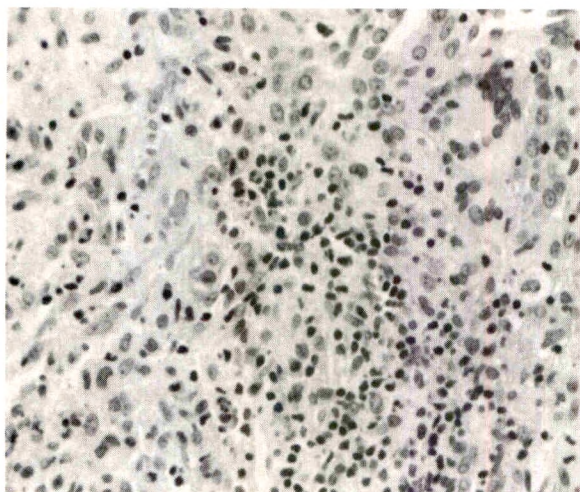


Fig. 2 (Sacks and associates). Case 2. Lung biopsy specimen. Left, Note aggregation of acute and chronic inflammatory cells admixed with giant cells (hematoxylin and eosin, $\times 225$). Right, Evidence of destructive vasculitis with disruption of the elastic wall in a pulmonary artery (Weigert's elastic tissue stain with Van Gieson counterstain, $\times 225$).

matory cells responsible for it originate distant from the eye, treatment with systemic corticosteroids or noncorticosteroid antiinflammatory agents are often effective. Patients unable to tolerate corticosteroids or unresponsive because of the intense nature of the local granulomatous response may benefit from cytotoxic agents.^{19,20} The condition in our first patient did not respond to topical medication for scleritis but did improve on oral prednisone. The systemic manifestations progressed, despite treatment with systemic corticosteroids, and finally resolved when cyclophosphamide was added. Cyclophosphamide therapy is considered the preferred drug for Wegener's granulomatosis because of its proven efficacy.²¹⁻²³ The condition in our second patient, who had bilateral, less severe scleritis, demonstrated a rapid response to initial combination treatment with corticosteroids and cyclophosphamide.

The findings in our two patients suggest that scleritis in children should prompt thorough investigation for an underlying systemic disorder. Treatment with systemic corticosteroids and possibly immunosuppressive drugs is likely to be necessary. With early initiation of appropriate therapy, the prognosis for scleritis associated with Wegener's granulomatosis in children appears to be good.

References

1. Stock, E. L., Rich, K., and Bouchard, C.: Scleritis in children. A report of three cases. *Intern. Med. Specialist* 8:104, 1987.
2. Berger, B., and Reeser, F.: Retinal pigment epithelial detachments in posterior scleritis. *Am. J. Ophthalmol.* 90:604, 1980.
3. Hayreh, S. S., and Watson, P. G.: Prednisolone-21-stearoylglycolate in scleritis. *Br. J. Ophthalmol.* 54:394, 1970.
4. Carrington, C. B., and Liebow, A. A.: Limited forms of angiitis and granulomatosis of Wegener's type. *Am. J. Med.* 41:497, 1966.
5. Straatsma, B. R.: Ocular manifestations of Wegener's granulomatosis. *Am. J. Ophthalmol.* 44:789, 1957.
6. Haynes, B. F., Fishman, M. L., Fauci, A. S., and Wolff, S. M.: The ocular manifestations of Wegener's granulomatosis. Fifteen years' experience and review of the literature. *Am. J. Med.* 63:131, 1977.
7. Bullen, C. L., Liesegang, T. J., McDonald, T. J., and DeRemee, R. A.: Ocular complications of Wegener's granulomatosis. *Ophthalmology* 90:279, 1983.
8. Hodges, E. J., Turner, S., and Doud, R. B.: Refractory scleritis due to Wegener's granulomatosis. *West. J. Med.* 146:361, 1987.
9. Brubaker, R., Font, R. L., and Shepherd, E. M.: Granulomatous sclerouveitis. Regression of ocular lesions with cyclophosphamide and prednisone. *Arch. Ophthalmol.* 86:517, 1971.
10. Vogiatzis, K. V.: Bilateral blindness due to necrotizing scleritis in a case of Wegener's granulomatosis. *Ann. Ophthalmol.* 15:185, 1983.
11. Parelhoff, E. S., Chavis, R. M., and Friendly, D. S.: Wegener's granulomatosis presenting as orbital pseudotumor in children. *J. Pediatr. Ophthalmol. Strabismus* 22:100, 1985.
12. Hall, S. L., Miller, L. C., Duggan, E., Mauer, S. M., Beatty, E. C., and Hellerstein, S.: Wegener's granulomatosis in pediatric patients. *J. Pediatr.* 106:739, 1985.
13. Halstead, L. A., Karmody, C. S., and Wolff, S. M.: Presentation of Wegener's granulomatosis in young patients. *Otolaryngol. Head Neck Surg.* 94:368, 1986.
14. Mohanlal, D., Meyers, K. E. C., Van Niekerk, I., and Richards, G. A.: Wegener's granulomatosis in an 11 year old child. *S. Afr. Med. J.* 73:608, 1988.
15. Lachman, S. M., Hazleman, B. L., and Watson, P. G.: Scleritis and associated disease. *Br. Med. J.* 1:88, 1978.
16. Watson, P. G., and Hayreh, S. S.: Scleritis and episcleritis. *Br. J. Ophthalmol.* 60:163, 1980.
17. Watson, P. G.: The diagnosis and management of scleritis. *Ophthalmology* 87:716, 1980.
18. Rao, N. A., Marak, G. E., and Hidayat, A. A.: Necrotizing scleritis. A clinicopathologic study of 41 cases. *Ophthalmology* 92:1542, 1985.
19. Jampol, L. M., West, C., and Goldberg, M. F.: Therapy of scleritis with cytotoxic agents. *Am. J. Ophthalmol.* 86:266, 1978.
20. Foster, C. S.: Immunosuppressive therapy for external ocular inflammatory disease. *Ophthalmology* 87:140, 1980.
21. Fauci, A. S., and Wolfe, S. M.: Wegener's granulomatosis. Studies in 18 patients and a review of the literature. *Medicine* 52:535, 1973.
22. Wolff, S. M., Fauci, A. S., and Horn, R. G.: Wegener's granulomatosis. *Ann. Intern. Med.* 81:513, 1974.
23. Novack, S. N., and Pearson, C. M.: Cyclophosphamide therapy in Wegener's granulomatosis. *N. Engl. J. Med.* 284:938, 1971.

Nuclear Sclerotic Cataract After Vitrectomy for Idiopathic Epiretinal Membranes Causing Macular Pucker

George M. Cherfan, M.D., Ronald G. Michels, M.D.†, Serge de Bustros, M.D.,
Cheryl Enger, M.S., and Bert M. Glaser, M.D.

We evaluated the occurrence or progression of nuclear sclerosis of the crystalline lens in 100 eyes after vitrectomy for removal of idiopathic epiretinal membranes causing macular pucker. The follow-up period ranged from six to 99 months (average, 29 months). Visually significant nuclear sclerosis was present preoperatively in three of the operated on eyes and four of the fellow eyes. The rate of occurrence or progression of visually significant nuclear sclerosis was far greater in the operated on eyes ($P < .0001$). Of 100 patients, 80 operated on eyes and 24 fellow eyes had visually significant nuclear sclerosis or had undergone previous cataract extraction at the conclusion of the study. Different concentrations of glucose in the intraocular irrigating solution did not affect occurrence of later nuclear sclerosis. Patients older than 50 years of age had a far greater incidence of later nuclear sclerosis than patients younger than 50 years of age ($P = .0003$). Nuclear sclerosis may be caused by altered lens metabolism after removal of part of the vitreous gel, since nuclear sclerosis also occurs in other conditions associated with vitreous liquefaction.

PARS PLANA VITRECTOMY methods are used to treat various types of posterior segment diseases, and surgery is often required in phakic as well as in aphakic and pseudophakic eyes.

Serious posterior segment complications are infrequent, and the most common postoperative complication is later progressive nuclear sclerosis of the crystalline lens. Cataract changes occur after vitrectomy for various conditions,¹⁻³ but postoperative cataract has been studied most extensively after surgery for macular pucker.⁴⁻⁸ De Bustros and associates⁹ previously reported the type and incidence of postoperative lens opacities after vitrectomy to remove idiopathic epiretinal membranes causing macular pucker.

We studied an expanded series of these patients with a longer follow-up period. We also evaluated the incidence of postoperative cataract in patients of different ages and in two groups of eyes in which different compositions of intraocular irrigating solution were used.

Patients and Methods

We reviewed 103 consecutive records of idiopathic epiretinal membranes affecting the macula in phakic eyes, which had been treated by vitrectomy and removal of the epiretinal tissue. The patients had no history of previous ocular surgery and no known ocular disease, other than macular pucker and posterior vitreous detachment in most eyes. Only patients with an intact crystalline lens in both eyes were included, thereby permitting comparison between both lenses of the same patient. One 10-year-old boy was excluded because of long-term high-dose corticosteroid therapy for a separate systemic condition. The patient developed posterior subcapsular cataracts in both eyes because of the corticosteroids, thereby masking any possible effect of vitrectomy. Two other patients were excluded because they lived in other countries, and a minimum of six months of follow-up could not be obtained. Thus, the study population was 100 patients.

Accepted for publication Dec. 28, 1990.

From the El Maghraby Eye Hospital, Jeddah, Saudi Arabia (Dr. Cherfan); The Retina Center at Saint Joseph Hospital, Baltimore, Maryland (Drs. Michels and Glaser); and Wilmer Ophthalmological Institute, Johns Hopkins University, Baltimore, Maryland (Dr. de Bustros and Ms. Enger).

Reprint requests to Bert M. Glaser, M.D., The Retina Center at Saint Joseph Hospital, P.O. Box 20,000, Baltimore, MD 21284.

†Deceased Jan. 15, 1991.

There were 48 males and 52 females. The patients ranged in age from 4 to 81 years (mean, 62 years; median, 66 years) at the time of the operation. The right eye was involved in 49 patients, and the left eye was involved in 51 patients. The follow-up interval ranged from six months to 99 months (mean, 29 months; median, 24 months).

The vitrectomy techniques used to treat these patients have been previously reported.^{4,7,8,10,11} A previously existing posterior vitreous detachment was present in more than 90% of eyes, and the posterior one half to two thirds of the vitreous gel was removed. The epiretinal membrane was then removed with a vitreoretinal pick and intraocular forceps. The intraocular portion of the operation took approximately 15 minutes, and the volume of irrigating solution used was usually 25 to 75 ml.

During the first half of the study (52 patients), an irrigating solution with a glucose concentration of 500 mg/dl was used, as was customary for patients with diabetes. This was a special solution prepared by the hospital pharmacy that was similar to the glutathione-bicarbonate-Ringer's solution developed by Edelhauser and associates.¹²⁻¹⁴ During the second half of the study (48 patients), the glucose concentration of this solution was reduced to 100 mg/dl.

For each patient, factors related to the preoperative examination, operative procedure, and postoperative examination were tabulated. Factors recorded from the history and preoperative examination included age, sex, eye, visual acuity, type and severity of lens opacity, intraocular pressure, and posterior vitreous separation. Factors recorded from the operative procedure included the type of infusion solution used, intraoperative complications, and use of intraocular air. Items recorded from the postoperative record included any additional surgery, type and severity of any lens opacity, other postoperative complications, corrected postoperative visual acuity, final postoperative visual acuity, details of the fundus examination, and primary cause of any decrease in visual acuity occurring postoperatively.

The lens changes were characterized as to the location and severity based on slit-lamp biomicroscopy. The locations were designated as cortical or anterior subcapsular cataract, nuclear sclerosis, and posterior subcapsular cataract. The severity of lens opacities was graded as none, trace, mild, moderate, and severe. Lens opacities graded mild to severe were consid-

ered to be visually significant because they were associated with visual reduction of two or more Snellen lines in the fellow eyes with normal macular function.

Kaplan-Meier life table methods were used to compute the cumulative proportion of eyes with development or worsening of nuclear sclerosis over time since the operation. These survival curves were compared between groups using the Lee-Desu statistic.¹⁵

Results

Preoperatively the lens was clear or had only trace nuclear sclerosis in 97 of the operated on eyes and 96 of the fellow eyes. At the time of the final patient visit, a visually significant nuclear sclerotic cataract, or a history of previous cataract extraction, was present in 80 of the operated on eyes and 24 of the fellow eyes. Postoperatively, lens opacity changes were classified as follows: none, 15 operated on eyes and 49 fellow eyes; trace, five operated on eyes and 27 fellow eyes; mild, ten operated on eyes and 17 fellow eyes; moderate, 43 operated on eyes and five fellow eyes; and severe, 27 operated on eyes and two fellow eyes. Fourteen eyes in the surgical group had undergone cataract extraction and one of the fellow eyes had undergone cataract extraction.

The time interval between surgery and development, or worsening, of visually significant nuclear sclerosis was determined for both the operated on and nonoperated on fellow eyes by recording the number of months after the operation that significant lens changes were first noted. Development, or worsening, of nuclear sclerosis was defined as a change from a clear lens to mild nuclear sclerosis, trace nuclear sclerosis to moderate nuclear sclerosis, or an increase of at least one full class of severity for eyes with mild or moderate nuclear sclerosis preoperatively. The data are presented using Kaplan-Meier life table methods (Fig. 1). The rate of progression was significantly higher in the operated on eyes ($P < .0001$, Lee Desu statistic). By 24 months, 68.4% (95% confidence interval, 58.7% to 78.0%) of the operated on eyes showed significant progression compared to 12.8% (95% confidence interval, 5.5% to 20.0%) of the nonoperated on fellow eyes.

The possible effect of different intraocular irrigating solutions on development of nuclear sclerosis was evaluated by comparing the 52

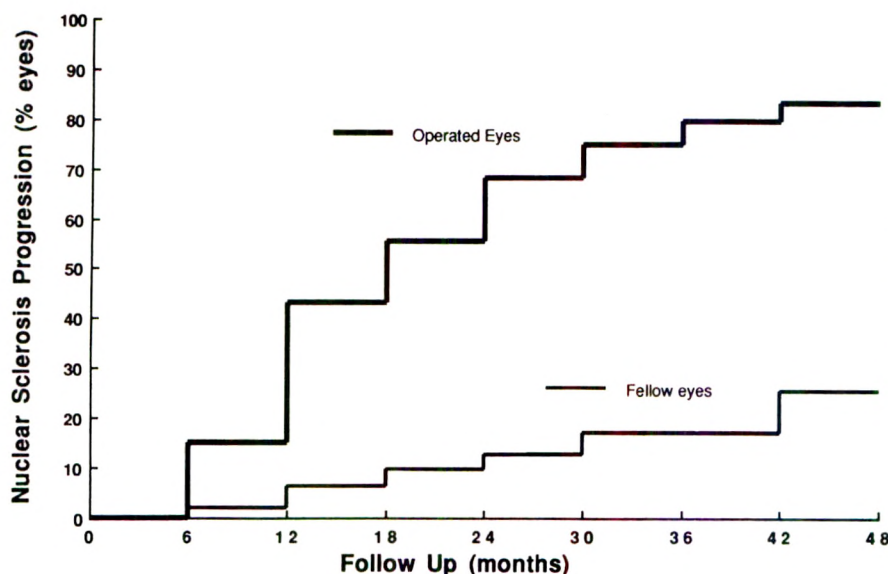


Fig. 1 (Cherfan and associates). Kaplan-Meier life table analysis showing significant difference in the rate of de novo development or progression of nuclear sclerosis in operated on eyes compared to fellow eyes ($P < .0001$).

eyes in which a hyperglycemic solution was used with those in which the glucose concentration was lower. Figure 2 compares the rate of progression of nuclear sclerosis between the two groups of operated on eyes and demonstrates no difference between the two ($P = .95$). There was a strongly significant difference, however, when comparing the occurrence of progressive nuclear sclerosis between the operated on eyes and the nonoperated on fellow eyes in each subgroup ($P < .0001$ for each).

The possible effect of patient age on development of postoperative nuclear sclerosis was evaluated by dividing the patients into those 50 years of age and younger ($N = 11$), and those older than 50 years of age ($N = 89$). The occurrence of later nuclear sclerosis in the operated on eyes is compared in Figure 3. The size of the groups was different, but only one of 11 patients in the younger group developed nuclear sclerosis, and the difference between the groups was significant ($P = .0003$).

Discussion

Vitreous surgery is now used to treat many types of posterior segment disease, and often surgery is performed in phakic eyes. Therefore, the occurrence of progressive postoperative cataract changes is an important consideration when surgery is contemplated. We studied the type and incidence of postoperative cataract in

eyes after removal of idiopathic epiretinal membranes causing macular pucker because these eyes had no other ocular diseases that could contribute to cataract formation, and the operation was especially brief. Therefore, cataract changes after vitrectomy could be attributed to changes induced by the operation, and the incidence of postoperative cataract would be known after the least invasive type of vitreous surgery operation.

Nuclear sclerosis is a common type of cataract associated with myopia and with advancing age. The origin of nuclear sclerosis is unknown, but it is caused by the gradual accumulation of insoluble lens proteins and pigments, which results in loss of transparency and color changes in the lens nucleus ranging from yellow to brown. When nuclear sclerosis occurs in patients without other ocular abnormalities or previous surgery, it is often nearly symmetric between the two eyes. Comparison between the operated on eyes and the fellow eyes in our patients demonstrated that progressive nuclear sclerosis was usually a sequela of surgery. There was also, however, a gradually increasing incidence of nuclear sclerosis in the fellow eyes related to aging.

An increased incidence of nuclear sclerosis has been demonstrated after vitrectomy for macular pucker, although the incidence has been found to range from 12.5%⁷ to 68%.⁸ Not all studies, however, have included only eyes with idiopathic epiretinal membranes. In eyes with other ocular diseases or other previous

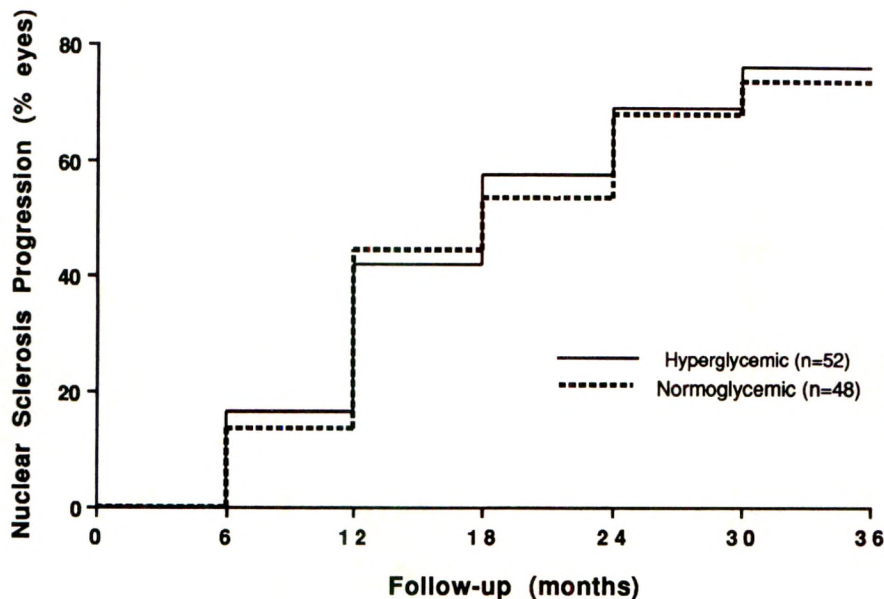


Fig. 2 (Cherfan and associates). Kaplan-Meier life table analysis showing no significant difference in the rate of de novo development or progression of nuclear sclerosis in the two groups of eyes based on whether a hyperglycemic or a normoglycemic irrigating solution was used during surgery.

surgical procedures, it is possible that these conditions contribute to the occurrence of cataract.

The cause of postoperative nuclear sclerotic lens opacities in our series is unknown. They could be related to the type of intraocular irrigating solution used during the vitrectomy. This seems unlikely, however, since we evaluated two solutions with different concentrations of glucose, and there was no difference in the incidence of later nuclear sclerosis. All other surgeons reporting postoperative nuclear sclerosis have used other commercially available irrigating solutions.

Other possible causes of nuclear sclerosis include light toxicity from the operating microscope or from the intraocular fiberoptic probe. Light toxicity could damage the lens directly or increase the intraocular temperature, which could result in lens damage. Permeability changes in the lens capsule induced by vitrectomy could also account for later changes in lens metabolism and nuclear sclerosis. Permeability changes seem most likely, since there is an increased incidence of nuclear sclerosis in severely myopic eyes and in patients with the Wagner-Stickler syndrome, both of which are associated with large fluid-filled spaces in the

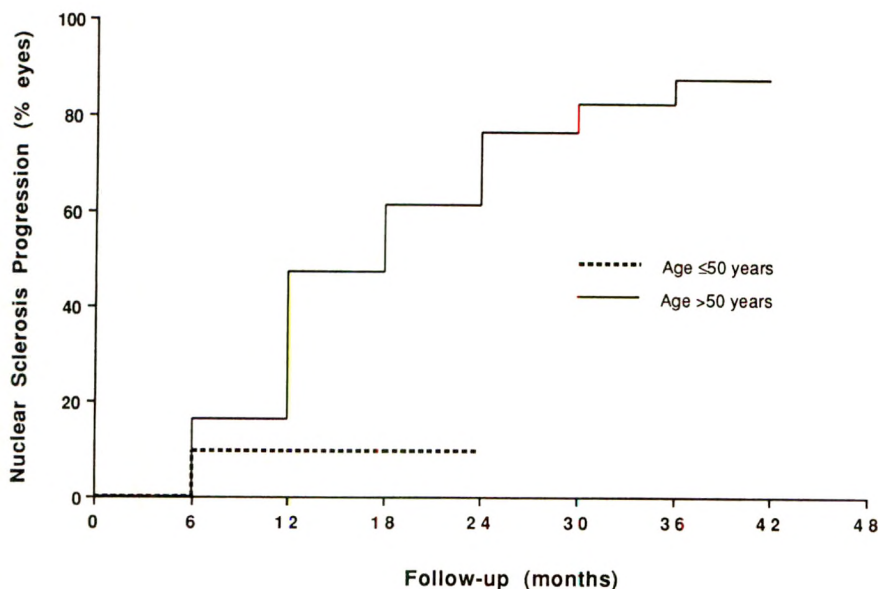


Fig. 3 (Cherfan and associates). Kaplan-Meier life table analysis showing significant difference in the rate of de novo development or progression of nuclear sclerosis in the operated on eyes of patients 50 years of age or younger compared to those older than 50 years ($P = .0003$).

vitreous cavity. Also, nuclear sclerosis occurs most frequently as an aging change after age 50 years when vitreous liquefaction is most evident.

No method is known to prevent nuclear sclerosis of the lens after pars plana vitrectomy. Sparing more of the vitreous gel behind the crystalline lens could be helpful. We made no effort to excise the anterior part of the vitreous gel, although postoperative slit-lamp examination often demonstrated little vitreous gel remaining behind the posterior lens capsule. Also, in patients undergoing pars plana vitrectomy for proliferative diabetic retinopathy, the incidence of later cataract was lower than in the current series,¹⁻³ even though the operation was usually longer and intraoperative and postoperative complications were more frequent in diabetic eyes. Part of this difference may be related to a younger average age of patients undergoing vitrectomy for complications of diabetic retinopathy. Still, our findings of occurrence or worsening of nuclear sclerosis after vitrectomy have important implications, especially in situations in which vitrectomy is selected as a therapeutic option, such as in treating primary rhegmatogenous retinal detachments. These observations also suggest that the origin of nuclear sclerotic cataract, occurring as an aging change in otherwise normal eyes, may be related to altered lens metabolism induced by vitreous liquefaction.

References

1. Schachat, A. P., Oyakawa, R. T., Michels, R. G., and Rice, T. A.: Complications of vitreous surgery for diabetic retinopathy. II. Postoperative complications. *Ophthalmology* 90:522, 1983.
2. Novak, M. A., Rice, T. A., Michels, R. G., and Auer, C.: The crystalline lens after vitrectomy for diabetic retinopathy. *Ophthalmology* 91:1480, 1984.
3. Hutton, W. L., Pesicka, G. A., and Fuller, D. G.: Cataract extraction in the diabetic eye after vitrectomy. *Am. J. Ophthalmol.* 104:1, 1987.
4. Michels, R. G.: Vitrectomy for macular pucker. *Ophthalmology* 91:1384, 1984.
5. de Bustros, S., Rice, T. A., Michels, R. G., Thompson, J. T., Marcus, S., and Glaser, B. M.: Vitrectomy for macular pucker after treatment of retinal tears or retinal detachment. *Arch. Ophthalmol.* 106:758, 1988.
6. de Bustros, S., Thompson, J. T., Michels, R. G., Rice, T. A., and Glaser, B. M.: Vitrectomy for idiopathic epiretinal membranes causing macular pucker. *Br. J. Ophthalmol.* 72:692, 1988.
7. Margherio, R. R., Cox, M. S., Jr., Trese, M. T., Murphy, P. L., Johnson, J., and Minor, L. A.: Removal of epimacular membranes. *Ophthalmology* 92:1075, 1985.
8. Poliner, L. S., Olk, R. J., Grand, M. G., Escoffery, R. F., Okun, E., Boniuk, I., and Farber, M. J.: Predictive variables in surgical management of premacular fibroplasia. *Arch. Ophthalmol.* 106:761, 1988.
9. de Bustros, S., Thompson, J. T., Michels, R. G., Enger, C., Rice, T. A., and Glaser, B. M.: Nuclear sclerosis after vitrectomy for idiopathic epiretinal membranes. *Am. J. Ophthalmol.* 105:160, 1988.
10. McDonald, H. R., Verre, W. P., and Aaberg, T. M.: Surgical management of idiopathic epiretinal membranes. *Ophthalmology* 93:978, 1986.
11. Michels, R. G.: *Vitreous Surgery*. St. Louis, C. V. Mosby, 1981, pp. 357-362.
12. Edelhauser, H. F., Van Horn, D. L., Hyndiuk, R. A., and Schultz, R. O.: Intraocular irrigating solutions. Their effect on the corneal endothelium. *Arch. Ophthalmol.* 93:648, 1975.
13. Edelhauser, H. F., Van Horn, D. L., Schultz, R. O., and Hyndiuk, R. A.: Comparative toxicity of intraocular irrigating solutions on the corneal endothelium. *Am. J. Ophthalmol.* 81:473, 1976.
14. Edelhauser, H. F., Gonnering, R., and Van Horn, D. L.: Intraocular irrigating solutions. A comparative study of BSS Plus and lactated Ringer's solution. *Arch. Ophthalmol.* 96:516, 1978.
15. Lee, E., and Desu, M.: A computer program for comparing k samples with right-censored data. *Comput. Programs Biomed.* 2:315, 1972.

Ultrastructural Study of Norrie's Disease

Laura Barlow Enyedi, B.S., Eugene de Juan, Jr., M.D., and Alicia Gaitan, B.S.

We studied the clinicopathologic and ultrastructural features of a full-term infant with Norrie's disease. The infant had bilateral retrolental fibrous vascular masses and retinal detachment with no other apparent physical abnormalities and no family history of ocular defects. A vitrectomy and a membrane peeling were attempted, and specimens of the retina, the retrolental membrane, and a vascularized epiretinal peripheral mass were examined by light and electron microscopy. The retrolental membrane was composed of layered collagenous tissue and contained structures resembling blood vessels. Inner and outer neuroblastic layers were identified in the retinal tissue, but no vessels were present. In the epiretinal mass, portions of retina and cortical vitreous were seen along with primitive vascular structures. The histologic appearance of these specimens suggests that the major pathologic event of Norrie's disease occurs in the retina in the third to fourth gestational month. We believe the subsequent ocular abnormalities found in this patient were secondary to this early retinal malformation and did not represent a progressive ocular disorder.

NORRIE'S DISEASE is a rare X-linked recessive condition characterized by congenital and presumed progressive oculo-acoustic-cerebral degeneration. Blindness and bilateral white, vascularized, retrolental masses are usually noted shortly after birth, and patients often develop cataracts and opaque corneas in childhood. Approximately two thirds of patients with Norrie's disease demonstrate progressive mental

retardation of differing degrees, and 25% to 33% have sensorineural hearing loss of differing severities.¹

The pathogenesis of Norrie's disease is unknown, but Warburg¹ postulated that a biochemical defect disrupts the neuroectoderm in an early stage of development, which causes malformation of the organs derived from neuroectoderm, including the retina, central nervous system, and parts of the inner ear. She regarded the failure of the secondary vitreous to form properly and the persistence and proliferation of the primary vitreous as secondary to the retinal malformation. We provide a detailed description of the ultrastructural findings of the ocular tissue removed from a patient with Norrie's disease.

Case Report

A 1-week-old boy was referred to our institution in December 1987 for examination of bilateral leukocoria. The full-term infant was the product of a normal pregnancy and was delivered by cesarean section (performed because of previous cesarean sections). The mother had no history of drug or alcohol use and had received good prenatal care. There was no gestational illness or birth trauma, and the patient was an otherwise healthy infant.

Anterior segment examination disclosed a clear cornea and shallow anterior chamber in both eyes. Intraocular pressure by applanation tonometry was normal in each eye. Vascular retrolental fibrous masses were noted behind each lens (Fig. 1). The ciliary processes were elongated in the right eye, and there was a slight red reflex (Fig. 1, left). There was no red reflex in the left eye (Fig. 1, right). There was no view posteriorly to the retina in either eye. Ultrasound examination showed total retinal detachments bilaterally with large peripheral retinal folds (Fig. 2).

An examination under anesthesia disclosed a

Accepted for publication Dec. 10, 1990.

From the Department of Ophthalmology, Duke University Eye Center, Durham, North Carolina. This study was supported by National Institutes of Health research grant EY05903.

Reprint requests to Eugene de Juan, Jr., M.D., Duke University Eye Center, Box 3802, Durham, NC 27710.

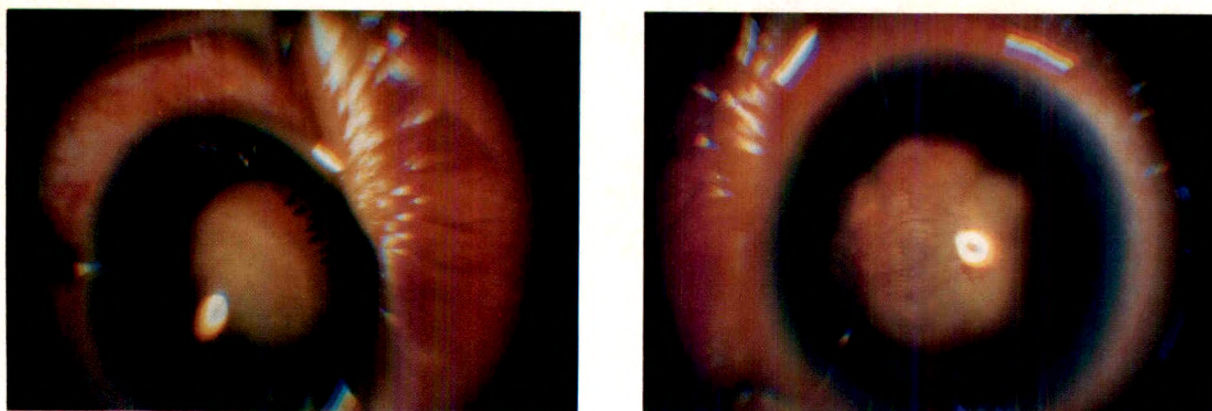


Fig. 1 (Enyedi, de Juan, and Gaitan). Left, Anterior segment of the right eye showing a red reflex that is caused by a trough in the periphery of the retina. The retrolental tissue is slightly vascularized and the ciliary processes are elongated and centrally drawn. Right, Left eye showing vascularized retrolental fibrous tissue.

retrolental vascularized membrane in the right eye that spread toward the ciliary body and was attached closely to the retina. The left eye had an appearance similar to the right eye with a central fibrous stalk that extended from behind the lens toward the ciliary body and a total retinal detachment with a slightly separated funnel posteriorly.

A lensectomy, vitrectomy, and membrane peeling were performed in the right eye. A large peripheral retinal fold (or trough) was found superiorly and temporally (Fig. 2, top). In the equatorial retina, there was a vascularized point of retinal thickening in which a vascularized mass appeared to be connected. This mass was vascularized from the vitreous rather than from the retinal circulation. The retina appeared totally avascular. The mass was excised and submitted for pathologic examination. Fibrovascular tissue from the retrolental space and a section of equatorial avascular retina were also submitted for examination.

One month postoperatively, the child did not respond to light in either eye. The anterior segment examination of the right eye disclosed a clear cornea. Fibrous tissue secluded the pupil, and there was no view posteriorly to the retina. Ultrasonography of the right eye disclosed persistent retinal elevation with a layered subretinal hemorrhage posteriorly. The left eye was unchanged. Subsequently, the left eye developed a cataract, a flat anterior chamber, and a hazy cornea. A lensectomy was later performed to prevent the development of glaucoma in the left eye.

The patient's mother and 4-year-old sister

were also examined. Results of ophthalmoscopic examinations were normal in both family members. The patient also had a 2-year-old sister, who was not examined but had normal vision. The family history disclosed no other ocular defects.

The patient has subsequently shown delays in both motor and speech and language development. His hearing was found to be normal by brainstem auditory-evoked response audiometry.

Results

The specimen obtained from the retrolental space consisted of a densely collagenous (collagen diameter of 23.5 nm and periodicity of 47.0 nm) hypocellular layered tissue (Fig. 3, left). The layers were separated from each other by polarized cells that in some instances contained a lumen (Fig. 3, right). The structures were not typical of blood vessels in mature tissues but may represent an abnormal vascular proliferation or persistence of hyaloidal vascular structures.

The specimen obtained from anterior retina was avascular and markedly disorganized. The outer neuroblastic layer (photoreceptor precursors) could be identified (Fig. 4), but inner and outer segments of photoreceptors were absent. The heterochromatin in these rectangular and irregularly shaped nuclei was distributed throughout the nucleus (Fig. 4, right). At the external limiting membrane there were small

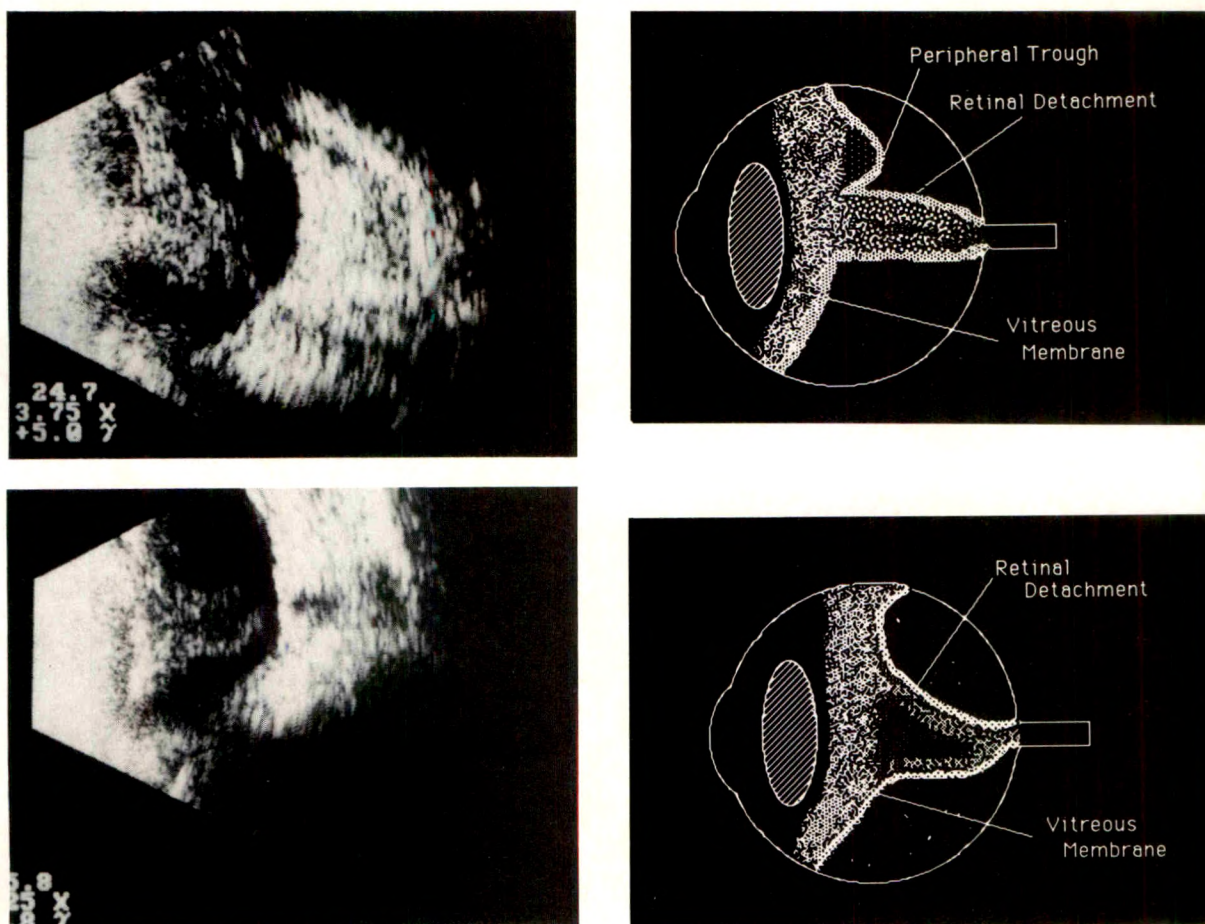


Fig. 2 (Enyedi, de Juan, and Gaitan). B-scan ultrasound (top left) and schematic drawing (top right) of the right eye shows that the retina is detached with peripheral folds (peripheral trough). Dense anterior vitreous echoes are present. Ultrasonogram (bottom left) and drawing (bottom right) of the left eye showing the total retinal detachment and vitreous membranes.

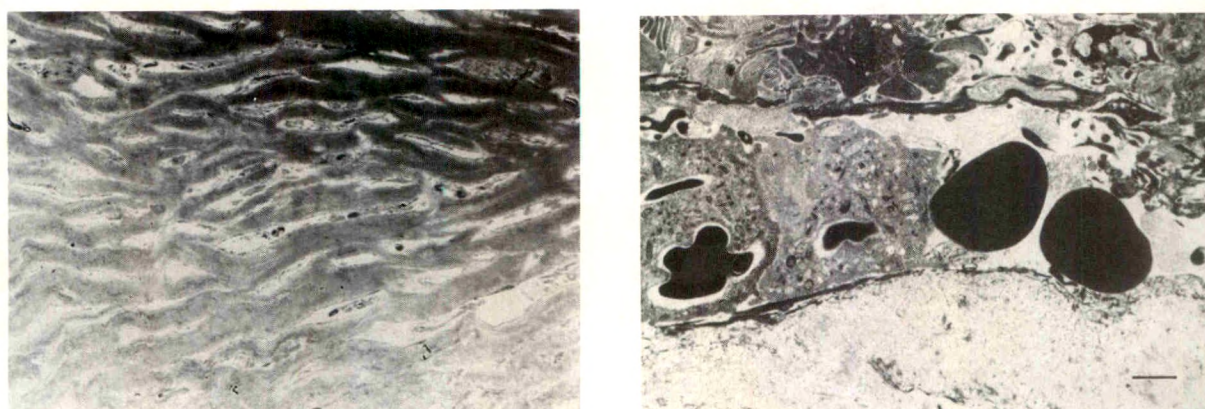


Fig. 3 (Enyedi, de Juan, and Gaitan). Left, The tissue obtained from the epiretinal membrane is composed of layered collagenous tissue. Polarized cells separate the layers (methylene blue and basic fuchsin, $\times 160$). Right, Electron micrograph of area resembling a vessel between collagen layers in the epiretinal membrane.

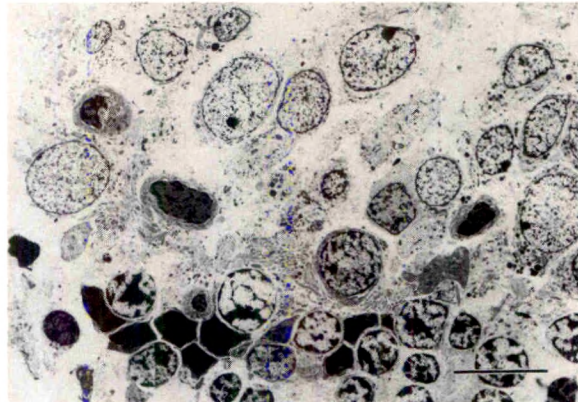
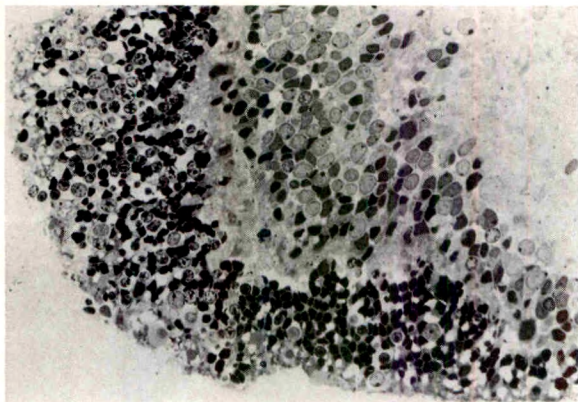


Fig. 4 (Enyedi, de Juan, and Gaitan). Left, The specimen obtained from the retina shows the darker-staining outer neuroblastic layer and lighter-staining inner neuroblastic layer (methylene blue and basic fuchsin, $\times 100$). Right, Electron micrograph of the retina showing the outer and inner neuroblastic layers. The smaller and electron-dense nuclei and the dark irregularly shaped nuclei (lower) from the outer neuroblastic layer probably represent photoreceptor precursors. The larger round and oval nuclei (upper) are part of the inner neuroblastic layer of the retina (bar equals 10 μm).

villous extensions, which may have been primitive outer segments of the photoreceptor precursors. Proximal to the outer neuroblastic layer was a thicker area of lighter-staining nuclei, which may have represented the inner neuroblastic layer of the retina. These nuclei were larger and contained less heterochromatin than the outer neuroblastic layer (Fig. 4). Their nucleoli were darkly stained (Fig. 4, right), and fibrils of 19.0 nm in diameter were present in the cytoplasm of these cells. There was a clear inner-limiting membrane present and a layer of dense collagenous fibrils internal to this (cortical vitreous) (Fig. 5).

The specimen obtained from the preretinal

vascular mass showed on one side the outer neuroblastic layer of the retina (Fig. 6, bottom). The nuclei of this layer were elongated, irregularly shaped, and contained dense heterochromatin (Fig. 7). Internal to the outer neuroblastic layer were groups of nuclei that resembled the inner neuroblastic layer of the developing retina. These nuclei were larger than those of the outer neuroblastic layer, were round or oval,



Fig. 5 (Enyedi, de Juan, and Gaitan). Electron micrograph of the retina shows the three-layer inner-limiting lamina that separates the retinal tissue (R) from the cortical vitreous (CV) (bar equals 1 μm).

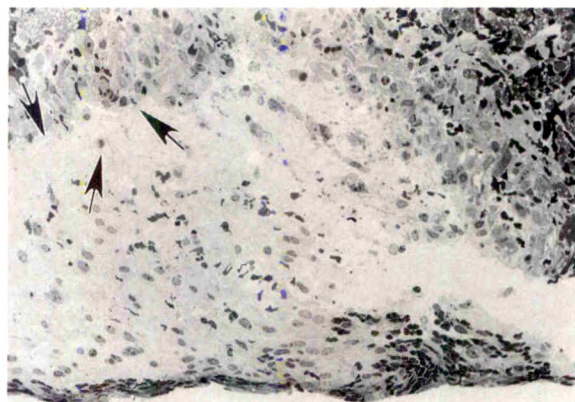


Fig. 6 (Enyedi, de Juan, and Gaitan). The preretinal fibrovascular mass with underlying retina. The outer neuroblastic layer of the retina is seen as a dark band at the bottom edge. The oval and round lighter-staining nuclei above the outer neuroblastic layer belong to the inner neuroblastic layer of the retina. Above the inner neuroblastic layer is a layer of cortical vitreous. An inner-limiting membrane (arrows) separates the cortical vitreous from vasoformative tissue and red blood cells (methylene blue and basic fuchsin, $\times 100$).

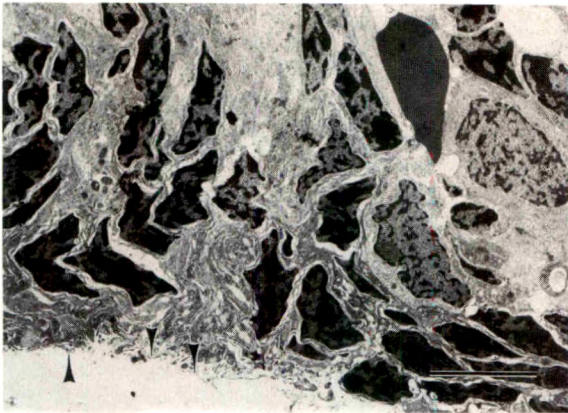


Fig. 7 (Enyedi, de Juan, and Gaitan). Electron micrograph of the irregularly shaped nuclei of the outer neuroblastic layer of the retina. The microvillous extensions (arrows) may represent attempts of the photoreceptor precursors to form primitive outer segments (bar equals 5 μ m).

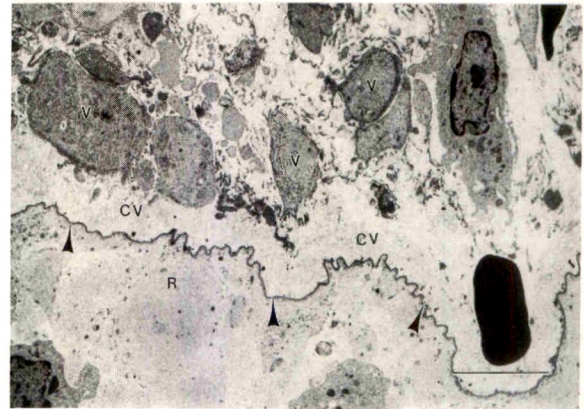


Fig. 8 (Enyedi, de Juan, and Gaitan). Electron micrograph of the retina subjacent to the preretinal tissue. The inner-limiting lamina (arrows) separates the retina (R) from the cortical vitreous (CV). Vasoformative tissue (V) lies internal to the cortical vitreous (bar equals 5 μ m).

and contained little heterochromatin (Fig. 6). A well-developed internal limiting lamina was present, and, along with a layer of cortical vitreous, it separated the poorly formed vascular tissue from the retina (Fig. 8). Rough endoplasmic reticulum and mitochondria were abundant in the vasoformative tissue. Central to the vasoformative tissue were many red blood cells, some surrounded by fibrin.

Discussion

The differential diagnosis of this patient included conditions commonly associated with leukocoria and infantile retinal detachment, such as persistent hyperplastic primary vitreous, retinopathy of prematurity, autosomal dominant familial exudative vitreoretinopathy, idiopathic retinal dysplasia, Patau's syndrome (trisomy 13), incontinentia pigmenti, and Norrie's disease.

Persistent hyperplastic primary vitreous usually occurs unilaterally and does not characteristically affect the retinal vasculature.^{2,3} The bilateral involvement of our patient was not typical of persistent hyperplastic primary vitreous, nor can the avascular retina of our patient be accounted for by persistent hyperplastic primary vitreous.

Since the patient was born at term, had a normal birth weight, and required no supplemental oxygen, his condition was not retinopathy

of prematurity. Although conditions have been reported that have a similar appearance to retinopathy of prematurity occurring in term infants without supplemental oxygen,⁴ we believe that these cases do not represent retinopathy of prematurity, despite the anatomic similarities. Moreover, although intrauterine factors (for example, cyanotic heart disease) could lead to a disease similar to retinopathy of prematurity in utero, these did not appear to exist in this child. Thus, we believe that without a typical history of prematurity or other risk factors, this and other such cases should not be classified as retinopathy of prematurity.

Familial exudative vitreoretinopathy rarely occurs in term infants and retinal vascular anomalies are usually found in the parents.⁵ No such anomalies were identified in the mother or sister of the patient. Moreover, avascular retina is not an associated finding in familial exudative vitreoretinopathy. Idiopathic retinal dysplasia occurs unilaterally, whereas our patient was affected bilaterally.⁶ Patau's syndrome causes severe nonocular anomalies, which were absent in our patient.⁷ Finally, incontinentia pigmenti is seen only in females, because it causes death in males in utero.^{8,9}

The most conspicuous sign of Norrie's disease is a dense, white, vascularized mass behind each lens. Blindness is usually observed early in infancy, followed by cataract formation and corneal degeneration in early childhood. Additionally, the eyes begin to shrink as the child grows older.¹ Other commonly observed

changes include vitreoretinal hemorrhages, retinal detachment, elongated ciliary processes, shallow anterior chambers, iris rubeosis, and iris atrophy.^{1,10-12} Our patient initially had congenital bilateral vascularized retrolental masses and bilateral congenital retinal detachments. The anterior chambers of both eyes were shallow, and the ciliary processes of the right eye were slightly elongated and centrally drawn (Fig. 1, left). The developmental delays observed in our patient are consistent with the diagnosis of Norrie's disease, and the normal hearing is not inconsistent with this diagnosis. Although there was no family history of Norrie's disease or other ocular diseases, the patient's condition seems characteristic of this rare disease.

Since the patient's condition resembled retinopathy of prematurity clinically, and because there was no view to the retina, a vitrectomy and membrane peeling were attempted. The severe immaturity of the retina was only fully appreciated subsequent to the operation and the histologic examination of the surgical specimens.

The specimens demonstrated the early cessation of retinal development characteristic of Norrie's disease, which supports Warburg's¹ belief that the ocular defects characteristic of Norrie's disease are the result of an early arrest in embryonic retinal development.

To determine how early in development this lesion occurred, it is helpful to consider the normal course of the embryonic development of the retina. By the third month of gestation, both the inner and outer neuroblastic layers have formed. The inner neuroblastic layer does not complete its differentiation into ganglion cells, amacrine cells, and Müller cells until the seventh month of gestation. The outer neuroblastic layer does not complete its differentiation into bipolar cells, horizontal cells, and nuclei of rods and cones until the seventh gestational month. Primitive rods and cones form between the third and seventh months of gestation.¹³ In the fourth gestational month, retinal blood vessels first emerge from the optic disk.¹⁴ In our patient, inner and outer neuroblastic layers were present with some degree of differentiation. Rod and cone nuclei precursors were identified in the outer neuroblastic layer, but no rods or cones were present. Furthermore, no blood vessels were found in the retina. Because of the presence of an inner neuroblastic layer, rod and cone precursors in the

outer neuroblastic layer, and the absence of blood vessels, we believe that some pathologic event occurred during the third to fourth gestational months.

The persistent hyaloidal vascular system probably occurred secondary to the retinal malformation and was the likely source of the fibrovascular retrolental masses.^{1,10} Persistence and hyperplasia of the primary vitreous were probably also responsible for associated ocular findings, such as retinal detachment and vitreoretinal hemorrhages.¹⁰ Finally, as noted by Apple, Fishman, and Goldberg,¹⁰ many of the later findings in Norrie's disease are not unique but rather are similar to those found in later stages of retinopathy of prematurity, persistent hyperplastic primary vitreous, and Patau's syndrome. These nonspecific changes include corneal decompensation, cataract, elongated and centrally displaced ciliary processes, shallow anterior chambers, and phthisis bulbi.

Warburg's¹ description of Norrie's disease as a progressive syndrome may not be completely accurate, particularly with regard to the ocular findings. The extent of mental and hearing changes is difficult to document in infancy. Moreover, these deficits become more evident as the child grows older. For at least the ocular changes, it would not appear that there is an ongoing degeneration. Rather, secondary changes occur as a result of an initial pathologic event to the embryonic retina.

References

1. Warburg, M.: Norrie's disease. A congenital progressive oculo-acousticocerebral degeneration. *Acta Ophthalmol.* 89:1, 1966.
2. Haddad, R., Font, R. L., and Reeser, F.: Persistent hyperplastic primary vitreous. A clinicopathologic study of 62 cases and review of the literature. *Surv. Ophthalmol.* 23:123, 1978.
3. Van Selm, J.: Surgery for retinal dysplasia and hyperplasia of the persistent primary vitreous. *Trans. Ophthalmol. Soc. U.K.* 89:545, 1970.
4. Karlsberg, R. C., Green, W. R., and Patz, A.: Congenital retrolental fibroplasia. *Arch. Ophthalmol.* 89: 122, 1973.
5. Tasman, W., and Augsburger, J. J.: Familial exudative vitreoretinopathy. *Trans. Am. Ophthalmol. Soc.* 79:211, 1981.
6. Hunter, W. S., and Zimmerman, L. E.: Unilateral retinal dysplasia. *Arch. Ophthalmol.* 74:24, 1965.
7. Miller, M., Robbins, J., Fishman, R., Medenis, R., and Rosenthal, I.: A chromosomal anomaly with

multiple ocular defects including retinal dysplasia. *Am. J. Ophthalmol.* 55:901, 1963.

8. Berbich, A., Dhermy, P., and Majbar, M.: Ocular findings in a case of incontinentia pigmenti (Bloch-Sulzberger syndrome). *Ophthalmologica* 182:119, 1981.

9. François, J.: Incontinentia pigmenti (Bloch-Sulzberger syndrome) and retinal changes. *Br. J. Ophthalmol.* 68:19, 1984.

10. Apple, D. J., Fishman, G. A., and Goldberg, M. F.: Ocular histopathology of Norrie's disease. *Am. J. Ophthalmol.* 78:196, 1974.

11. Nadol, J. B., Eavey, R. D., Liberfarb, R. M., Merchant, S. N., Williams, R., Climenhager, D., and Albert, D. M.: Histopathology of the ears, eyes, and

brain in Norrie's disease (oculoacousticocerebral degeneration). *Am. J. Otolaryngol.* 11:112, 1990.

12. Townes, P. L., and Roca, P. D.: Norrie's disease (hereditary oculo-acoustic-cerebral degeneration). Report of a United States family. *Am. J. Ophthalmol.* 76:797, 1973.

13. Mann, I.: The neural ectoderm. *The Development of the Human Eye*. New York, Grune & Stratton, 1964, p. 81.

14. van Nouhuys, C. E.: Development and anatomy of the normal vasculature of the peripheral retina. *Dominant Exudative Vitreoretinopathy and Other Vascular Developmental Disorders of the Peripheral Retina*. The Hague, Junk Publishers, 1982, p. 5.

OPHTHALMIC MINIATURE

"Lonesome Charley is no judge of bears," Jim said. "He's only got one eye. Of course, a bear will look bigger if you've only got one eye to look out of."

Bartle was making a stew as they talked. The stew consisted of a squirrel and a few wild onions. The squirrel had been so inept as to actually fall out of a tree. It had landed right at his feet and he had brained it with his gun stock. Jim's rejoinder took him so completely by surprise that for a moment he was speechless. Why would anyone suppose that the loss of one eye doubled the size of what one looked at? And yet, that seemed to be what his friend had suggested.

Larry McMurtry, *Buffalo Girls*
New York, Simon and Schuster, 1990, pp. 99 and 100

Relatively Enhanced S Cone Function in the Goldmann-Favre Syndrome

Samuel G. Jacobson, M.D., Alejandro J. Román, B.S., Marisa I. Román, B.S.,
J. Donald M. Gass, M.D., and John A. Parker, M.D.

Using electrophysiologic and psychophysical tests that measure rod, midspectral, and S (blue) cone function, we studied four patients with the Goldmann-Favre syndrome, an autosomal recessive vitreoretinal degeneration. With spectral electroretinography, the predominant signal was from the S cones. With dark-adapted perimetry, all patients had severely reduced rod sensitivities and subnormal midspectral cone sensitivities. With S cone perimetry, the patients had normal or subnormal S cone function. Sensitivity differences between S and midspectral cones were significantly different from normal; there was relatively higher sensitivity of S cones compared to midspectral cones throughout the visual field. This relationship of dysfunctional cone mechanisms in the Goldmann-Favre syndrome is similar to that in the enhanced S cone syndrome, a recently identified retinal degeneration with S cone hypersensitivity. The results suggest that the Goldmann-Favre and the enhanced S cone syndromes are linked by a common pattern of retinal dysfunction.

THE GOLDMANN-FAVRE SYNDROME, described in 1958,¹ is an autosomal recessive vitreoretinal degeneration characterized by night blindness,

pigmentary degeneration, macular and peripheral retinoschisis, posterior subcapsular cataract, markedly abnormal or nondetectable electroretinograms, and degenerative vitreous changes, such as liquefaction, strands, or bands. Since the original description, other cases have been reported,²⁻⁶ thereby confirming that this is a clinically recognizable entity. The underlying mechanisms of this disease, however, remain unclear.

Recently, a retinal degeneration was identified with an unusual pattern of retinal dysfunction.^{7,8} This retinopathy, the enhanced S cone syndrome, was so named because of the finding that the large amplitude atypical electroretinograms in these patients are mediated mainly by S (blue) cones, and there is evidence of S cone hypersensitivity by psychophysical testing. All of these patients have night blindness, and some patients have cystic changes in the macula.

The interesting coincidence of night blindness and cystic-appearing maculopathy in the two syndromes prompted us to study four patients with the Goldmann-Favre syndrome and compare the results of their retinal function tests with those of four patients with the enhanced S cone syndrome. Despite differences in clinical phenotype and severity of visual loss, all eight patients had the same functional phenotype as defined by a unique relationship between S cone and midspectral cone sensitivities. We propose that the Goldmann-Favre and enhanced S cone syndromes are not distinct entities but are simply recognizable phenotypes in a wider spectrum of clinical expression with a single pattern of retinal dysfunction.

Patients and Methods

Four patients with the Goldmann-Favre syndrome, four patients with the enhanced S cone

Accepted for publication Jan. 16, 1991.

From the Department of Ophthalmology, University of Miami School of Medicine, Bascom Palmer Eye Institute, Miami, Florida (Drs. Jacobson and Gass, Mr. Román, and Mrs. Román); and Department of Ophthalmology, University of Toronto, Toronto Hospital, Toronto, Ontario, Canada (Dr. Parker). This study was supported in part by Public Health Service research grant EY05627 (Dr. Jacobson), the National Retinitis Pigmentosa Foundation, Inc. (Baltimore, Maryland), and the Daniel Matzkin Fellowship for Study of Retinal Degenerations.

Reprint requests to Samuel G. Jacobson, M.D., Department of Ophthalmology, Bascom Palmer Eye Institute, P.O. Box 016880, Miami, FL 33101.

syndrome, and 24 normal subjects (seven men and 17 women, ages 19 to 56 years) participated in this study. The Goldmann-Favre syndrome was diagnosed according to previous clinical descriptions of the disease.¹⁻⁶ The patients with enhanced S cone syndrome, none of whom were included in our previous series of patients,^{7,8} met both clinical and electroretinographic criteria established for this diagnosis.⁸ Conventional full-field electroretinograms were performed according to published techniques.^{9,10} Goldmann kinetic perimetry was performed with a V_{4e} target on a 10-cd/m² white background; kinetic visual field area was quantified by a published method.⁹ Patients gave their informed consent to all procedures after full explanations were given.

Spectral electroretinograms were elicited in the dark- and light-adapted (34-cd/m² white background) states using a scotopically matched pair of stimuli (blue filter, Wratten 98, at intensity setting 1.50, and yellow-orange filter, Wratten 16, at setting 1.00) and a stimulus pair matched for the S cones (blue filter, Wratten 98, and blue-green filter, Wratten 44, both at setting 1.25).⁷ A photometer and spectrometer were used to measure the photopic flash luminances and their spectral content.⁷ The scotopic and S cone units for determining the matched pairs of stimuli were calculated.¹¹

Static threshold perimetry was performed with monochromatic test stimuli (all target diameters, 103 minutes) under different adaptation states using a modified automated perimeter.¹² Two-color, dark-adapted perimetry was performed with 500- and 650-nm stimuli. Whether rods, cones, or both mediated detection at each locus was determined from the sensitivity difference between the two stimulus colors.¹²⁻¹⁴ Dark-adapted sensitivities to 500- and 650-nm stimuli in normal subjects were measures of rod-mediated function at almost all extrafoveal loci.¹²⁻¹⁴ The patients had no rod-mediated loci but only cone-mediated or mixed rod- and cone-mediated function.⁷ For the patients, sensitivities to 500 nm, dark-adapted, were taken as estimates of rod function, and sensitivities to 650 nm, dark-adapted, were measurements of longer-wavelength cone function. Normal subjects were tested with 650 nm during the cone plateau of dark adaptation to compare with the patients' results with 650 nm, dark-adapted. S cone perimetry was performed with a 440-nm stimulus on a yellow adapting background (171 cd/m²).^{7,15,16}

Two test strategies were used for dark-

adapted and S cone perimetry: a full-field test of 76 loci on a 12-degree grid,¹² and a central-field test of 49 loci on a 4-degree grid covering a square region of 24 degrees on a side. The 125 sensitivities from the full-field and central-field test strategies were ordered by their eccentricity from the fovea; measurements at the same eccentricity, irrespective of meridian, were averaged; and the resulting 27 eccentricities were plotted along the horizontal axis from 0 (fixation or foveal locus) to 75 degrees.

Results

Clinical examination—The patients with Goldmann-Favre syndrome had either autosomal recessive inheritance (Cases 1 and 2) or were from multiplex (other affected siblings but no parental consanguinity) families (Cases 3 and 4; Table). On clinical examination, they had severe pigmentary retinal degeneration, retinoschisis, some posterior subcapsular cataract (or had undergone cataract surgery), and degenerative vitreous changes, mainly fibrillar strands and condensations. Vitreous liquefaction and bands were not present.⁴ All four patients had night blindness (at least 3 log units of rod sensitivity loss throughout the visual field by dark-adapted perimetry). Visual acuity varied from moderately impaired (Cases 3 and 4) to severely abnormal (Cases 1 and 2). Kinetic perimetry in Case 1 showed large central scotomas with the V_{4e} target, but the total field area with this target was within 2 standard deviations of the mean normal. Two patients (Cases 2 and 4) had reduced visual field area because of extensive midperipheral scotomas or peripheral field defects; one patient (Case 3) had only a small island in the central visual field and an island in the far temporal peripheral field.

The patients with enhanced S cone syndrome had autosomal recessive inheritance (Case 8) or were from multiplex (Case 5) or simplex (the only affected member) families (Cases 6 and 7). In three of the patients, the only fundus abnormalities were cystic changes in the macula with or without yellow flecks. One patient (Case 5) had pigment clumping and atrophy localized around the vascular arcades. There were no lens opacities, and no vitreous abnormalities were noted other than some cells. All four patients had night blindness, and the three patients who were tested with dark-adapted perimetry had at least 3 log units of rod sensi-

TABLE
CLINICAL CHARACTERISTICS OF THE PATIENTS

CASE NO., FAMILY NO., AGE (YRS), SEX	GENETIC TYPE	EYE	VISUAL ACUITY	KINETIC FIELD AREA (%)*	FUNDUS ABNORMALITIES†
Goldmann-Favre Syndrome					
1, 1, 46, F	Autosomal recessive	R.E. L.E.	6/200 2/200	90	Macula, R.E.: pigment clumping and atrophy; macula, L.E.: scar; superficial cysts and deep yellow lesions throughout retina
2, 1, 55, F	Autosomal recessive	R.E. L.E.	20/200 20/200	57	Cystic maculopathy; pigment clumping and atrophy beyond vascular arcades; peripheral retinoschisis
3, 2, 40, M	Multiplex	R.E. L.E.	20/30 20/40	7	Bone spicule-like pigment, pigment clumping and atrophy around and beyond vascular arcades; opaque peripheral retinal vessels; peripheral retinoschisis
4, 3, 36, F	Multiplex	R.E. L.E.	20/30 20/60	71	Pigment clumping and atrophy around vascular arcades; peripheral retinoschisis‡
Enhanced S Cone Syndrome					
5, 3, 35, M	Multiplex	R.E. L.E.	20/25 20/25	97	Yellow flecks in macula and periphery; pigment clumping and atrophy around vascular arcades
6, 4, 33, M	Simplex	R.E. L.E.	20/60 20/70	93	Cystic maculopathy
7, 5, 25, M	Simplex	R.E. L.E.	20/200 20/200	91	Cystic maculopathy; yellow flecks in macula
8, 6, 49, F	Autosomal recessive	R.E. L.E.	NA§ NA	NA NA	Cystic maculopathy; yellow flecks below optic disk

*Expressed as a percent of normal mean; 2 standard deviations below normal = 90%⁹; value reported is for eye that had all the perimetric tests in this study.

†Similar in both eyes unless specified.

‡Peripheral retinoschisis treated with photocoagulation at age 11 years; hyperpigmented scars are seen in this region currently.

§NA indicates not available, because psychophysical tests were not performed reliably.

tivity loss throughout the visual field. Visual acuity varied from nearly normal (Case 5) to severely subnormal (Case 7). Kinetic visual field area with the V_{4e} target was within the normal range in the three patients tested.

Electroretinography—Figure 1 shows the pattern of electroretinograms in the dark- and light-adapted states in a normal subject, a patient with enhanced S cone syndrome, and a patient with Goldmann-Favre syndrome. In the normal subject, dark-adapted responses to white light flashes over this intensity range were suprathreshold and appeared to saturate at the highest intensities. The typical difference between normal dark- and light-adapted waveforms was present: the larger and slower dark-adapted signals represent combined rod and

cone activity, and the smaller and faster light-adapted signals are cone responses.¹⁷

All patients with enhanced S cone syndrome showed a pattern of responding to the white light stimuli that differed dramatically from normal. The pattern is exemplified by the electroretinograms of Case 8 (Fig. 1). The lowest intensity white light stimulus in the dark-adapted state was below threshold; with higher intensities the responses increased in amplitude but did not saturate. Unlike the normal electroretinograms, the electroretinograms of Case 8 under dark- and light-adapted conditions were similar in waveform shape, although the light-adapted signals were lower in amplitude. All patients with enhanced S cone syndrome had generally similar waveform shapes

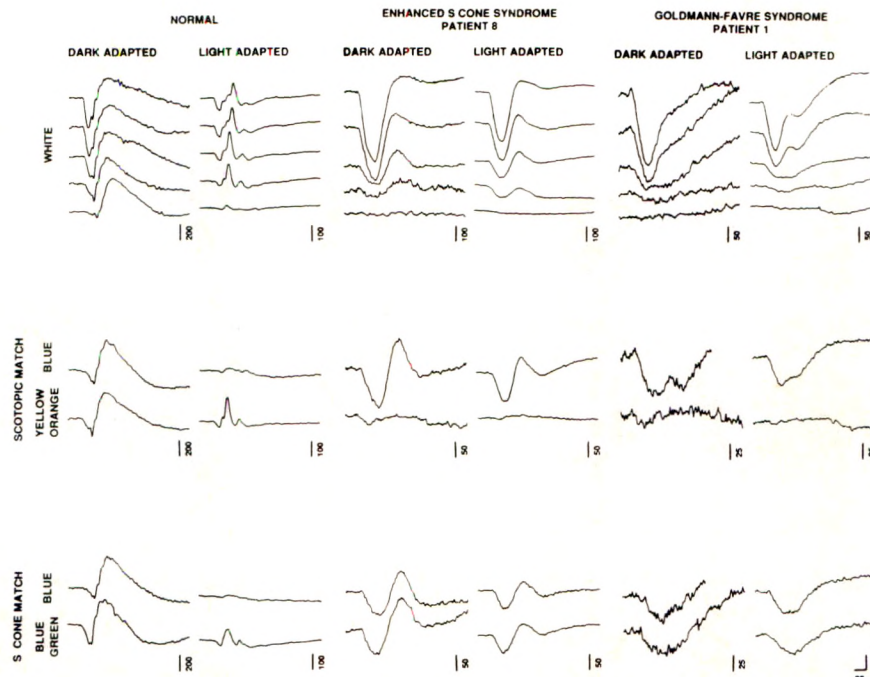


Fig. 1 (Jacobson and associates). Electrophoretograms elicited in a normal subject (left), patient with enhanced S cone syndrome (Case 8; middle), and patient with Goldmann-Favre syndrome (Case 1; right). Top, The two sets of five responses each are to increasing intensities of white light in the dark- and light-adapted states; relative log units (from top to bottom) are: 0, -0.2, -0.7, -1.0, and -1.8. Middle, The next two responses for each subject are to blue and yellow-orange light flashes that are scotopically matched (1.7 log scotopic troland-second). Bottom, The lowest two responses are to blue and blue-green light flashes that are matched for the S cones. Amplitude calibrations (vertical bars, microvolts) are at the lower right of each set of responses; the timing calibration (horizontal bar, milliseconds) for all responses is at the extreme right. Stimulus onset occurs 20 msec after trace onset.

with both negative and positive components (amplitudes of positivity were 200 to 350 μV for maximum intensity white light flash, dark-adapted, compared with a normal mean of 470 μV and one standard deviation of 112 μV). The negative component of the waveform of Case 8 became especially prominent at higher intensities.

Patients with Goldmann-Favre syndrome showed a range of electroretinogram amplitudes from sizable (Cases 1 and 2; 150 and 30 μV , respectively, of positivity to maximum white light, dark-adapted) to barely measurable (Case 4) to nondetectable (Case 3). The responses in Case 1 to white light stimuli were mainly negative, and the waveforms were similar under dark- and light-adapted conditions (Fig. 1). The responses in Case 2 had the same characteristics but were smaller in amplitude. This pattern was the same as in the patients with enhanced S cone syndrome, and it differed remarkably from normal.

Chromatic stimuli in the dark- and light-

adapted states clarified which photoreceptor-mediated mechanisms were responsible for the waveforms elicited with white light stimuli (Fig. 1). Scotopically matched blue and yellow-orange stimuli in the dark-adapted state evoked responses of similar amplitude in the normal subject. In the light-adapted state, there was a much larger signal to yellow orange than to blue, as expected with these rod-matched stimuli, since the responses are derived mainly from the midspectral cones.¹⁷⁻²⁰ In both the patients with enhanced S cone syndrome and the patients with Goldmann-Favre syndrome, the rod-matched stimuli were mismatched in the dark- and light-adapted states, with much larger and slower responses to blue than to yellow-orange stimuli occurring under both states of adaptation.⁷ This indicated that the waveforms were not mediated mainly by the rods.

S cone-matched blue and blue-green stimuli did not elicit matched responses in the normal subject under either dark- or light-adapted conditions (Fig. 1). In contrast, both patients had

well-matched responses to these stimuli in both the dark- and the light-adapted states (the dark-adapted responses to blue green were slightly larger in amplitude, which suggested there might have been a contribution from the rod system⁷). These results indicate that the electroretinograms in the patients with enhanced S cone syndrome and Goldmann-Favre syndrome were mediated predominantly by the S cone system.

Psychophysics—Figure 2 shows results of rod (500 nm, dark-adapted), midspectral cone (650 nm, dark-adapted), and S cone (440 nm, yellow background) perimetry plotted against eccentricity in normal subjects, one patient with the enhanced S cone syndrome, and three patients with the Goldmann-Favre syndrome.

The patient with enhanced S cone syndrome (Case 6) showed at least 3 log units of rod sensitivity loss across the visual field. Midspectral cone sensitivity was reduced slightly more than 2 standard deviations below the mean normal at almost all eccentricities. S cone sensitivities are normal in the central 10 degrees and higher than normal at most other eccentricities. The results in Case 7 were similar to those in Case 6, except the central area of normal S cone

sensitivities extended to about 25 degrees. The results in Case 5 differed by showing some S cone hypersensitivity and normal midspectral cone sensitivity in the central 10 degrees and a scotomatous region for all mechanisms between about 15 and 30 degrees (corresponding to the localized fundus pigmentary change, Table).

In the patients with enhanced S cone syndrome, S cone function in the central 30 degrees of visual field was usually normal or supernormal, or both. Beyond the central 30 degrees, there was S cone hypersensitivity at more than two thirds of the test loci with most of the remaining loci showing normal sensitivity. Only a few central and peripheral loci had subnormal S cone sensitivity in patients with this diagnosis.

Patients with Goldmann-Favre syndrome had more severe dysfunction than patients with enhanced S cone syndrome (Fig. 2). In Case 1, for example, there were markedly subnormal rod and midspectral cone sensitivities in the central 30 degrees and slightly better function, albeit still subnormal, at greater eccentricities. S cone sensitivities were subnormal centrally but fell within the normal range in the periph-

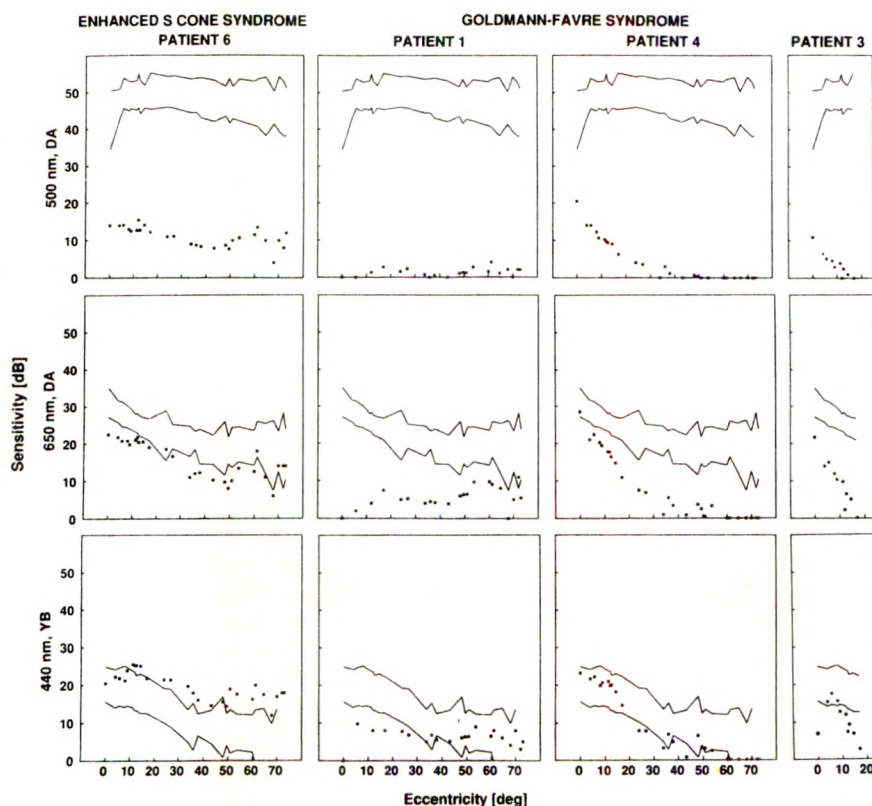


Fig. 2 (Jacobson and associates). Sensitivities (decibels, dB) at different eccentricities (degrees, deg) to 500-nm (upper panels) and 650-nm (middle panels) stimuli, dark-adapted (DA), and to 440 nm on a yellow background (YB, lower panels) in a patient with enhanced S cone syndrome (Case 6) and three patients with Goldmann-Favre syndrome (Cases 1, 4, and 3; data in Case 3 corrected for aphakia¹¹). Solid lines are data for ten normal subjects (ages 19 to 56 years) and delimit 2 standard deviations above and below the mean normal.

eral field. The findings in Cases 3 and 4 differed from those in Case 1 in the regional retinal distribution of the disease. Central function was severely reduced for rods but only slightly subnormal for midspectral cones and within the normal range for S cones. In Case 4, there was measurable sensitivity to an eccentricity of about 50 degrees, but in Case 3, function was limited to a relatively small central island.

In the patients with Goldmann-Favre syndrome, there was mainly normal and subnormal S cone function throughout the visual field. Except for a few loci in the peripheral field of one patient, there was no S cone hypersensitivity in patients with this diagnosis.

Even though patients with Goldmann-Favre syndrome showed little or no S cone hypersensitivity, we noted that S cone sensitivities appeared to be relatively higher than midspectral cone sensitivities, an abnormal relationship of cone mechanisms, which is the opposite of what has been reported to occur in other ocular diseases.^{15,21} This effect was also evident in regions of the visual field without S cone hypersensitivity in the patients with enhanced S cone syndrome. We hypothesized that there may be a predictable relationship between S cone and midspectral cone function in both enhanced S cone and Goldmann-Favre syndrome, independent of the level of dysfunction. To test the hypothesis, we calculated the sensitivity differences between 440 nm on the yellow adapting field and 650 nm in the dark-adapted state at all test loci with measurable function.

The sensitivity differences between S cones and midspectral cones in the two groups of patients are plotted in Figure 3 as a function of eccentricity and compared with normal data. In normal subjects, the sensitivity differences averaged about -10 dB at most eccentricities. The patients with enhanced S cone syndrome and the Goldmann-Favre syndrome could have a normal sensitivity difference at the foveal locus, but at all other eccentricities the differences clustered near 0 dB, more than 2 standard deviations higher than the mean normal. Even in the presence of severe visual loss, the relationship between S cone and midspectral cone function differed significantly from normal.

Discussion

We have shown that two clinically recognizable phenotypes, the Goldmann-Favre syn-

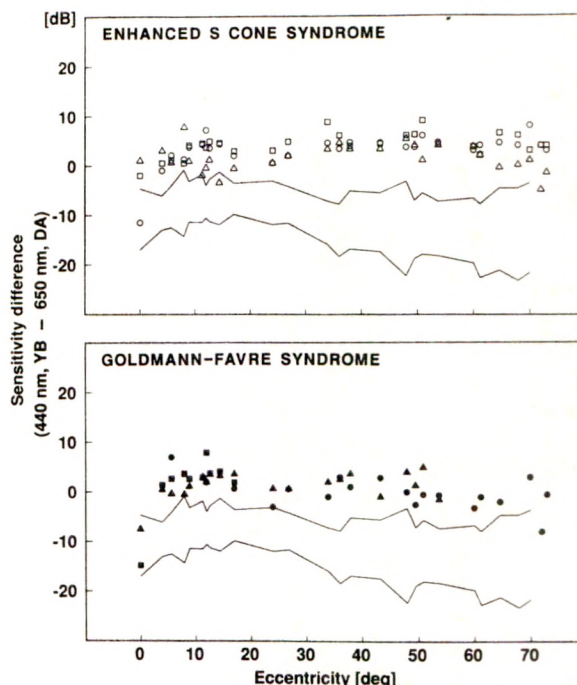


Fig. 3 (Jacobson and associates). Sensitivity differences between 440 nm on a yellow background (YB) and 650 nm, dark-adapted (DA), at different eccentricities for patients with enhanced S cone syndrome (top) and Goldmann-Favre syndrome (bottom). Case 1, filled circles; Case 2, filled triangles; Case 3, filled squares (corrected for aphakia¹¹); Case 5, unfilled circles; Case 6, unfilled squares; and Case 7, unfilled triangles. Solid lines are normal data that delimit 2 standard deviations above and below the mean normal sensitivity differences.

drome and the enhanced S cone syndrome, share a pattern of retinal dysfunction defined by a unique relationship between S cone and midspectral cone function. With electroretinography to white light stimuli, patients from both diagnostic categories had abnormal waveforms that were similar under dark- and light-adapted conditions. With spectral electroretinography, the pattern of results in all patients with measurable signals was the same and suggested relatively greater S cone than midspectral cone function. Furthermore, psychophysical testing showed an identical relationship between S cone and midspectral cone sensitivities in patients with enhanced S cone and Goldmann-Favre syndrome independent of the dimension of their visual field and the severity of dysfunction within it. Another clue that the enhanced S cone and Goldmann-Favre syndromes are related comes from finding the

two syndromes in one family. In Family 3, one sibling fulfilled diagnostic criteria for the enhanced S cone syndrome and the other for the Goldmann-Favre syndrome.

Our results show sufficient overlap in clinical and functional characteristics of the two diagnostic categories to warrant the speculation that the Goldmann-Favre and enhanced S cone syndromes are not distinct entities but simply two identifiable phenotypes in a wide spectrum of clinical expression of retinal degenerative disease with a single pattern of retinal dysfunction. The clinical expression varies from apparently localized macular or paravascular degenerative changes to extensive central and peripheral retinal degeneration with retinoschisis and vitreous degeneration. All patients had night blindness, but regional retinal variation of severity of the disease led to a range of abnormalities in visual function from mild visual acuity losses to large central scotomas, from nearly full visual fields to tunnel vision, and from supernormal light-adapted electroretinograms to nondetectable signals under any condition.

Further understanding of the complete spectrum of clinical and functional manifestations of this retinopathy will occur with identification of other patients. To distinguish definitively this retinopathy from other disorders, some method to assess S cone function and relate it to midspectral cone function is required. A number of clinically feasible techniques for S cone electroretinography and S cone perimetry have been described.^{15,16,21-23} These techniques have mainly been used to investigate various ocular diseases that manifest reduced S cone function relative to midspectral cone function, the opposite pattern to what we have found in this study. Two methods, one electroretinographic⁸ and the other perimetric,²⁴ have been used for diagnosis of the enhanced S cone syndrome and may be more convenient in a clinical setting than the techniques that isolate individual photoreceptor mechanisms. Both these electroretinographic and perimetric screening tests use the same general principle: a short-wavelength stimulus and a longer-wavelength stimulus were selected to produce equal responses in normal subjects under light-adapted conditions, and these stimuli in patients with enhanced S cone syndrome elicited unequal responses, with better responses occurring to the shorter-wavelength stimulus.^{8,24} We applied this electroretinographic test to two patients with Goldmann-Favre syndrome (Cases 1 and

2) and the perimetric test to two patients (Cases 2 and 3), and the tests proved sensitive enough to detect the dysfunctional mechanism even in these relatively severely affected patients.

This study cannot answer the question of whether the different clinical phenotypes with this autosomal recessively inherited pattern of retinal dysfunction are variations in expression of a single gene defect or examples of genetic heterogeneity. This awaits determination of the exact cellular and molecular bases of the relatively higher sensitivity of S cone to midspectral cone function in these patients.

ACKNOWLEDGMENT

William J. Feuer, M.S., provided the statistical analysis.

References

1. Favre, M.: A propos de deux cas de degenerescence hyaloideoretinienne. *Ophthalmologica* 135:604, 1958.
2. Ricci, A.: Clinique et transmission hereditaire des degenerescences vitreo-retiniennes. *Bull. Soc. Ophthalmol. Fr.* 61:618, 1961.
3. François, J., de Rouck, A., and Cambie, E.: Degenerescence hyaloideo-tapeto-retinienne de Goldmann-Favre. *Ophthalmologica* 168:81, 1974.
4. Fishman, G. A., Jampol, L. M., and Goldberg, M. F.: Diagnostic features of the Favre-Goldmann syndrome. *Br. J. Ophthalmol.* 60:345, 1976.
5. Hirose, T., Schepens, C. L., Brockhurst, R. J., Wolf, E., and Tolentino, F. I.: Congenital retinoschisis with night blindness in two girls. *Ann. Ophthalmol.* 12:848, 1977.
6. Nasr, Y. G., Cherfan, G. M., Michels, R. G., and Wilkinson, C. P.: Goldmann-Favre maculopathy. *Retina* 10:178, 1990.
7. Jacobson, S. G., Marmor, M. F., Kemp, C. M., and Knighton, R. W.: SWS (blue) cone hypersensitivity in a newly identified retinal degeneration. *Invest. Ophthalmol. Vis. Sci.* 31:827, 1990.
8. Marmor, M. F., Jacobson, S. G., Foerster, M. H., Kellner, U., and Weleber, R. G.: Diagnostic clinical findings of a new syndrome with night blindness, maculopathy, and enhanced S cone sensitivity. *Am. J. Ophthalmol.* 110:124, 1990.
9. Jacobson, S. G., Yagasaki, K., Feuer, W. J., and Román, A. J.: Interocular asymmetry of visual function in heterozygotes of X-linked retinitis pigmentosa. *Exp. Eye Res.* 48:679, 1989.
10. Yagasaki, K., and Jacobson, S. G.: Cone-rod dystrophy. Phenotypic diversity by retinal function testing. *Arch. Ophthalmol.* 107:701, 1989.

11. Wyszecki, G., and Stiles, W. S.: *Color Science. Concepts and Methods, Quantitative Data and Formulae*, ed. 2. New York, John Wiley & Sons, 1982.
12. Jacobson, S. G., Voigt, W., Parel, J.-M., Apáthy, P. P., Nghiem-Phu, L., Myers, S. W., and Patella, V. M.: Automated light- and dark-adapted perimetry for evaluating retinitis pigmentosa. *Ophthalmology* 93:1604, 1986.
13. Massof, R. W., and Finkelstein, D.: Rod sensitivity relative to cone sensitivity in retinitis pigmentosa. *Invest. Ophthalmol. Vis. Sci.* 18:263, 1979.
14. Apáthy, P. P., Jacobson, S. G., Nghiem-Phu, L., Knighton, R. W., and Parel, J.-M.: Computer-aided analysis in automated dark-adapted perimetry. In Greve, E. L., and Heijl, A. (eds.): *Seventh International Visual Field Symposium*. Dordrecht, The Netherlands, Martinus Nijhoff Publishers/Dr. W. Junk Publishers, 1987, pp. 279-284.
15. Sample, P. A., and Weinreb, R. N.: Color perimetry for assessment of primary open-angle glaucoma. *Invest. Ophthalmol. Vis. Sci.* 31:1869, 1990.
16. Johnson, C. A., Adams, A. J., Twelker, J. D., and Quigg, J. M.: Age-related changes in the central visual field for short-wavelength-sensitive pathways. *J. Opt. Soc. Am.* 5:2131, 1988.
17. Gouras, P.: Electroretinography. Some basic principles. *Invest. Ophthalmol.* 9:557, 1970.
18. Gouras, P., Eggers, H. M., and MacKay, C. J.: Cone dystrophy, nyctalopia and supernormal rod responses. A new retinal degeneration. *Arch. Ophthalmol.* 101:718, 1983.
19. Gouras, P., MacKay, C. J., Ivert, L., Mittl, R., Neuwirth, J., and Eggers, H.: Computer-assisted spectral electroretinography in vitrectomy patients. *Ophthalmology* 92:83, 1985.
20. Gouras, P., MacKay, C. J., Evers, H., and Eggers, H.: Computer assisted spectral electroretinography (CASE). A tool for examining hereditary retinal degenerations. In Hollyfield, J., and LaVail, M. (eds.): *Retinal Degeneration. Experimental and Clinical Studies*. New York, Alan R. Liss, Inc., 1985, pp. 115-130.
21. Greenstein, V. C., Hood, D. C., Ritch, R., Steinberger, D., and Carr, R. E.: S (blue) cone pathway vulnerability in retinitis pigmentosa, diabetes and glaucoma. *Invest. Ophthalmol. Vis. Sci.* 30:1732, 1989.
22. Sawusch, M., Pokorny, J., and Smith, V. C.: Clinical electroretinography for short wavelength sensitive cones. *Invest. Ophthalmol. Vis. Sci.* 28:966, 1987.
23. Gouras, P., and MacKay, C. J.: Electroretinographic responses of the short-wavelength-sensitive cones. *Invest. Ophthalmol. Vis. Sci.* 31:1203, 1990.
24. Milam, A. H., and Jacobson, S. G.: Photoreceptor rosettes with blue cone opsin immunoreactivity in retinitis pigmentosa. *Ophthalmology* 97:1620, 1990.

OPHTHALMIC MINIATURE

Christmas in the jungle passed virtually unnoticed, with the usual problems unabated: there were more desertions among the porters, the going was difficult, and eye problems seemed to strike almost everyone, an "unpleasant phenomenon," as Burton called the affliction.

"My companion . . . now began to suffer from an inflammation of a low type, affecting the whole of the interior tunic of the eyes, particularly the iris, the choroid coat, and the retina; he described it as an almost total blindness, rendering every object enclouded as by a misty veil."

Edward Rice, *Captain Sir Richard Francis Burton*
New York, Macmillan, 1990, p. 299

Early-Onset Autosomal Dominant Retinitis Pigmentosa With Severe Hyperopia

Byron L. Lam, M.D., and G. Frank Judisch, M.D.

We studied a four-generation family with early-onset autosomal dominant retinitis pigmentosa, severe hyperopia, and axial eye lengths of less than 20 mm. The affected members had decreased vision, night blindness, typical peripheral retinal pigmentary changes, and electroretinographic abnormalities characteristic of retinitis pigmentosa. This pedigree suggests there is another variant of retinitis pigmentosa associated with hyperopia besides Leber's congenital amaurosis and preserved para-arteriole retinal pigment epithelium.

EXCEPT FOR PATIENTS with Leber's congenital amaurosis and those with preserved para-arteriole retinal pigment epithelium, patients with retinitis pigmentosa almost always have myopia.¹⁻⁴ We treated a family with early-onset autosomal dominant retinitis pigmentosa and moderate to severe hyperopia with short axial eye lengths.

Patients and Methods

Five affected members of a family with retinitis pigmentosa have been examined at our institution since 1969. A thorough family history was obtained. The inheritance pattern was consistent with autosomal dominant disease (Fig. 1). Four affected members (III-4, IV-7, IV-8, and IV-9) were followed up for at least five years.

Accepted for publication Jan. 8, 1991.

From the Department of Ophthalmology, University of Iowa, Iowa City, Iowa. This study was supported in part by an unrestricted grant to the Department of Ophthalmology from Research to Prevent Blindness, Inc.

Reprint requests to G. Frank Judisch, M.D., Department of Ophthalmology, University of Iowa Hospitals and Clinics, Iowa City, IA 52242.

Current information on Patient II-2 was obtained locally. Complete ophthalmic examinations, including keratometry and ultrasonic axial eye length measurements, were performed on the four affected members and four other nonaffected members (II-3, III-2, III-3, and IV-3). Goldmann visual fields, electroretinograms, and dark adaptation were performed on some affected family members.

Results

The five affected members had decreased central and night vision (Table). Visual fields were constricted, scotopic electroretinograms were nonrecordable, and dark adaptation thresholds were increased. Fundus changes characteristic of retinitis pigmentosa, including patchy retinal pigment epithelium depigmentation, cystoid macular edema with an inner retinal hole, pigment clumping (bone spicules), early optic atrophy, and vascular attenuation, were noted (Fig. 2). The onset of symptoms and signs of the

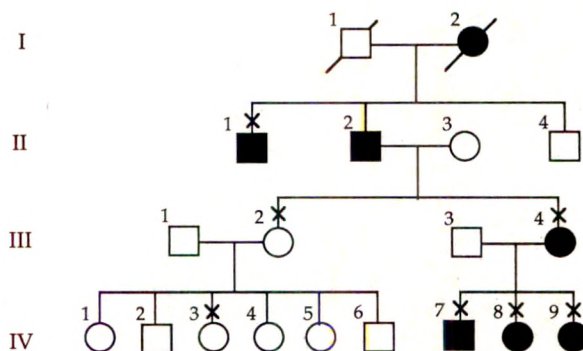


Fig. 1 (Lam and Judisch). Pedigree of family with retinitis pigmentosa associated with hyperopia. Squares indicate males and circles indicate females; solid symbols indicate affected; a slash through the symbol indicates deceased; an X above the symbol indicates examined.

TABLE
DATA ON TEN MEMBERS OF A FAMILY WITH RETINITIS PIGMENTOSA*

PATIENT NO.	DATE OF LAST EXAMINATION	AGE (YRS)	VISUAL ACUITY	CYCLOPLEGIC REFRACTION	KERATOMETRY	AXIAL EYE LENGTH (MM)	GOLDMANN VISUAL FIELDS	ELECTRORETINOGRAM
II-1†	9/69	41	LP 20/70	Mature cataract Aphakia	NA	NA	NA	NA
II-2†	4/89	65	LP HM	Aphakia Aphakia	NA	NA	NA	NA
II-3	7/90	54	20/25 20/25	+2.25 +1.50 × 85 +4.00 sphere	43.00 × 45.50 × 90 43.50 × 45.00 × 99	21.21 21.23	NA	NA
III-2	6/90	37	20/20 20/20	-3.00 +1.00 × 90 -1.75 +0.25 × 90	44.00 × 45.75 × 93 44.25 × 45.50 × 92	23.46 22.97	NA	NA
III-3	7/89	39	20/20 20/20	Plano +0.25 sphere	44.25 × 45.00 × 90 44.25 × 45.00 × 90	23.27 23.17	NA	NA
III-4†	6/90	31	20/40 20/50	+4.00 +1.50 × 90 +4.25 +1.00 × 90	45.00 × 47.75 × 92 45.00 × 47.00 × 92	19.35 19.25	Constricted Constricted	Nonrecordable Scotopic electroretinogram
IV-3	7/90	12	20/20 20/20	Plano Plano	43.25 × 44.25 × 99 43.50 × 43.75 × 100	23.21 22.94	NA	NA
IV-7†	6/90	16	20/30 20/30	+3.75 +2.00 × 90 +4.00 +2.00 × 85	45.50 × 47.75 × 95 45.00 × 48.00 × 92	19.60 19.60	Constricted Constricted	Nonrecordable Scotopic electroretinogram
IV-8†	6/89	11	20/30 20/40	+8.25 +1.50 × 92 +8.25 +1.25 × 90	45.75 × 47.75 × 90 45.75 × 47.75 × 90	17.91 17.89	Constricted Constricted	Dark adaptation Increased 2.0 log units
IV-9†	12/89	9	20/40 20/40	+6.50 +2.00 × 105 +7.25 +2.00 × 95	46.25 × 49.50 × 90 46.25 × 49.50 × 90	18.39 18.21	NA	NA

*LP indicates light perception and HM indicates hand motions. NA indicates not available.

†Affected members.

retinitis pigmentosa occurred in the first decade in all patients.

The four affected members (III-4, IV-7, IV-8, and IV-9) had moderate to severe hyperopia. The mean spherical equivalent was +6.61 diopters (standard deviation, 1.97 diopters) as com-

pared to +0.39 diopters (standard deviation, 2.16 diopters) for the four unaffected members (II-3, III-2, III-3, and IV-3). Other unaffected members did not wear spectacles. The axial eye lengths of the four affected spectacles were all less than 20 mm, which suggests that much of

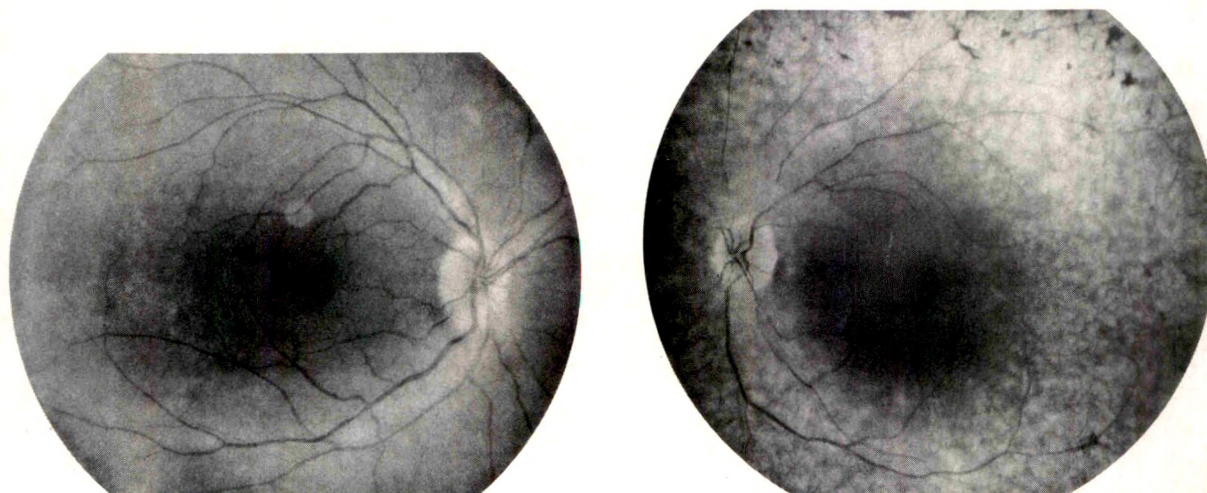


Fig. 2 (Lam and Judisch). Left, Patient IV-9 at age 9 years showing early foci of depigmentation and a cysticlike fovea with inner retinal hole. Right, Patient III-4 at age 31 years showing prominent patchy depigmentation with granularity, peripheral pigment clumping (bone spicules), retinal vascular narrowing, and early optic atrophy.

the hyperopia was probably axial. Although Patient II-3 was somewhat hyperopic, her axial eye length was greater than 21 mm.

Patients II-1 and II-2 developed cataracts in the fifth decade and had aphakia. They had worn thick magnifying spectacles before cataract development and most probably had hyperopia also.

Discussion

With two exceptions, patients with Leber's congenital amaurosis and those with preserved para-arteriole retinal pigment epithelium, patients with retinitis pigmentosa almost invariably have myopia.^{1,4} Sieving and Fishman³ found that myopia occurred in 201 of 268 eyes with retinitis pigmentosa (75%) as compared to 12% in a normal population, and the refractive errors ranged from +4.50 to -16.25 diopters.

Hyperopia has been suggested as a feature to distinguish retinitis pigmentosa from Leber's congenital amaurosis, because patients with Leber's congenital amaurosis usually have moderate to severe hyperopia.^{1,5,6} Likewise, patients with retinitis pigmentosa with preservation of para-arteriole retinal pigment epithelium are the only other exception to the association between myopia and retinitis pigmentosa. Both Leber's congenital amaurosis and preserved para-arteriole retinal pigment epithelium are usually autosomal recessive disorders.^{2,5}

All affected members available for examination had moderate to severe hyperopia with spherical equivalents of greater than 4.50 diopters. Two others had hyperopia by history. Although the retinitis pigmentosa in this family tended to manifest itself in the first decade, none of the affected members had features of Leber's congenital amaurosis,⁷ such as apparent blindness from early infancy or nystagmus, and visual acuities were all better than 20/50. There was no evidence of preserved para-arteriole retinal pigment epithelium.

Additionally, the affected family members had axial eye lengths of less than 20 mm. Mackay and associates⁸ described seven patients from a kinship who all had nanophthalmos, cystic macular degeneration, and angle-

closure glaucoma. The inheritance pattern, however, was autosomal recessive. Hermann⁹ described a family with autosomal dominant occurrence of nanophthalmos, angle-closure glaucoma, and retinal degeneration. The affected members all had myopia.

Hyperopia is a useful clinical sign in distinguishing most cases of retinitis pigmentosa from Leber's congenital amaurosis. Our pedigree, however, shows that early-onset autosomal dominant retinitis pigmentosa may be associated with hyperopia, which further supports the consensus of genetic heterogeneity in retinitis pigmentosa. Further study is necessary to determine if this pedigree is an example of close linkage between retinitis pigmentosa and hyperopia genes or of other as yet unappreciated factors.

References

1. Wagner, R. S., Caputo, A. R., Nelson, L. B., and Zanoni, D.: High hyperopia in Leber's congenital amaurosis. *Arch. Ophthalmol.* 103:1507, 1985.
2. Heckenlively, J. R.: Preserved para-arteriole retinal pigment epithelium in retinitis pigmentosa. *Br. J. Ophthalmol.* 66:26, 1982.
3. Sieving, P. A., and Fishman, G. A.: Refractive errors of retinitis pigmentosa patients. *Br. J. Ophthalmol.* 62:163, 1978.
4. Heckenlively, J. R.: *Retinitis Pigmentosa*. Philadelphia, J. B. Lippincott, 1988, p. 75.
5. Foxman, S. G., Heckenlively, J. R., Batemen, J. B., and Wirtshafter, J. D.: Classification of congenital and early-onset retinitis pigmentosa. *Arch. Ophthalmol.* 103:1502, 1985.
6. Lambert, S. R., Kriss, A., Taylor, D., Coffey, R., and Pembrey, M.: Follow-up and diagnostic reappraisal of 75 patients with Leber's congenital amaurosis. *Am. J. Ophthalmol.* 107:624, 1989.
7. Smith, D., Oestreicher, J., and Musarella, M. A.: Clinical spectrum of Leber's congenital amaurosis in the second to fourth decades of life. *Ophthalmology* 97:1156, 1990.
8. Mackay, C. J., Shek, M. S., Carr, R. E., Yanuzzi, L. A., and Gouras, P.: Retinal degeneration with nanophthalmos, cystic macular degeneration, and angle closure glaucoma. *Arch. Ophthalmol.* 105:366, 1987.
9. Hermann, P.: Le syndrome microphthalmie-retinite pigmentaire-glaucoma. *Arch. Ophthalmol.* 18:17, 1958.

Corneal Ulcer and Adverse Reaction Rates in Premarket Contact Lens Studies

Scott MacRae, M.D., Carol Herman, B.S., R. Doyle Stulting, M.D.,
Richard Lippman, O.D., David Whipple, B.S., Elisabeth Cohen, M.D.,
Donald Egan, O.D., Charles P. Wilkinson, M.D., Clifford Scott, O.D.,
Ronald Smith, M.D., and Dave Phillips, Ph.D.

We analyzed clinical data on 22,739 contact lens wearers who were studied and whose lenses were approved under 48 manufacturer-sponsored studies for the Food and Drug Administration between 1980 and 1988. The incidence of corneal ulcers was low in the cosmetic (nontherapeutic) daily-wear soft and rigid gas-permeable lens wearers (1/1,923 and 1/1,471 patient-years, respectively). Corneal ulcers and severe adverse reactions occurred two to four times more frequently in extended-wear cosmetic soft and rigid gas-permeable lens wearers than in cosmetic daily-wear lens wearers. Aphakic extended-wear soft lens users were nine times more likely to develop a corneal ulcer when compared to the soft daily-wear cosmetic group. Corneal abrasions and keratitis accounted for 81 of 159 severe adverse reactions, whereas corneal ulcers accounted for 28 of 159 adverse reactions. The data indicate that overnight extended wear of contact lenses is associated with a greater risk of serious, sight-threatening complications than daily wear.

SINCE THEIR APPROVAL IN 1981, extended-wear soft lenses have been associated with an increase in complications, including an estimated 8,000 corneal ulcers per year.¹ The use of cosmetic extended-wear soft lenses represents a significant preventable public health problem in the United States.²

Accepted for publication Jan. 17, 1991.

From the Food and Drug Administration, Washington, D.C. This study was supported by Research to Prevent Blindness, Inc., and the Oregon Corneal Research Fund.

Reprint requests to Scott MacRae, M.D., Oregon Health Sciences University, Department of Ophthalmology, 3181 S.W. Sam Jackson Park Rd., Portland, OR 97201.

We reviewed summary reports on 22,739 patients who were being periodically observed in Food and Drug Administration premarket approval investigations. These studies provided an estimate of the relative frequency of serious, sight-threatening complications induced by contact lenses. The studies took place over an eight-year period (1980 through 1988) and included daily- and extended-wear soft and rigid gas-permeable contact lens groups who wore these lenses for cosmetic (nontherapeutic) or aphakic indications. Soft and rigid gas-permeable lenses are classified by the Food and Drug Administration as class III devices. Class III devices require a premarket approval investigation for Food and Drug Administration approval. All 48 lenses studied are currently approved by the Food and Drug Administration after premarket approval investigations. We evaluated five major contact lens categories with the exception of polymethylmethacrylate lenses, which are class I devices. Class I devices do not require a premarket approval investigation.

Patients and Methods

Food and Drug Administration premarket approval investigations are initiated when a contact lens manufacturer wishes to obtain Food and Drug Administration approval of a new contact lens. The manufacturer will provide data regarding the relative safety and efficacy of the new contact lens by performing a study on several hundred eyes over a fixed period of time (usually three to 24 months). The patients are monitored with scheduled ocular examinations at regular intervals, and the findings are documented and submitted at each visit for the manufacturers to tabulate.

We reviewed 48 consecutive contact lens pre-market approval applications and Food and Drug Administration summary reports submitted between 1980 and 1988, which were recommended for approval by the Food and Drug Administration's Ophthalmic Devices Panel. The contact lenses were categorized into five groups: daily-wear soft, daily-wear rigid gas-permeable, extended-wear soft, extended-wear rigid gas-permeable, and aphakic extended-wear soft.

The first four groups wore lenses for cosmetic indications, including the correction of hyperopia, myopia, and astigmatism. The aphakic extended-wear soft contact lens group wore lenses for visual rehabilitation after cataract surgery.

Inclusion criteria for the cosmetic lens studies were determined by each individual manufacturer. In general, the subjects had healthy eyes. Patients with preexisting ocular diseases, such as glaucoma, uveitis, and the like, were excluded. Patients could have worn lenses previously. Generally, younger adults were included in the cosmetic lens studies when compared to the aphakic group. Direct age comparisons, however, were not possible.

Patients with aphakia were enrolled into the study as determined by the practitioner. Manufacturers generally encouraged practitioners to select patients with otherwise healthy eyes; however, patients with underlying ocular diseases may have been entered at the discretion of

the physician after considering the patients' needs.

Overall, patient completion rates were determined by dividing the number of patients who completed the study by the number of patients enrolled. Patients who did not complete the study were generally in one of two categories. The first category included those patients who were discontinued from the study because of inability to wear the lenses, disinterest, or an adverse reaction. The second category included those who were enrolled in the study but who did not finish the study because the manufacturer had enough patients to fulfill Food and Drug Administration requirements. Data from both groups who did not complete the study were included in the analysis. Since this is how the data were and are currently reported to the Food and Drug Administration, subset data comparing patients who discontinued and completed the studies are not available.

Definitions—Adverse reactions were defined as a serious, sight-threatening complication (Table 1). Corneal ulcers were defined as a break in the corneal epithelium with a surrounding gray or white opacity. Corneal infiltrates were defined as faint, gray or white corneal opacities with or without faint overlying staining but with the overlying epithelium still intact.

The 1988 Food and Drug Administration slit-lamp classification scale (guidance document for class III contact lenses) was used to define

TABLE 1
SEVERE ADVERSE REACTIONS

CONTACT LENS GROUP	CORNEAL ULCER	SEVERE UVEITIS/IRITIS	SEVERE CORNEAL ABRASION/KERATITIS	CORNEAL INFILTRATE	SEVERE PANNUS SCARRING	SEVERE CORNEAL EDEMA	SEVERE VASCULARIZATION	OTHER
Daily soft (N = 8)	1	—	4	3	—	—	—	—
Daily rigid gas permeable (N = 6)	1	—	3	—	—	—	2	—
Extended soft (N = 64)	13	1	22	1	2	—	5	20
Extended rigid gas permeable (N = 21)	3	1	11	3	—	—	1	2
Aphakic extended soft (N = 60)	10	—	41	—	—	6	—	3
Total (N = 159)	28	2	81	7	2	6	8	25

the complications. Corneal abrasion, keratitis, or both were defined as grade III (moderate, corneal staining defined as significant dense coalesced staining or abrasion or foreign body tracks) or grade IV (severe, corneal staining defined as severe abrasions or epithelial loss of full-thickness abrasion) corneal staining. Severe corneal neovascularization was defined as segmented or circumscribed extensions of limbal vessels more than 2.5 mm inside the corneal scleral limbus or extension to within 3.0 mm of the corneal apex. Severe corneal edema was defined as advanced localized or generalized edema with more than 50 vacuoles (microcysts), epithelial bullae, epithelial sloughing, or a combination of these. Severe iritis and uveitis were defined as marked cells, flare, or both in the anterior chamber. Severe pannus was not defined in the 1988 guidelines but was reported by several investigators. Adverse reactions were categorized based on the findings noted in the premarket approval report. If a serious, sight-threatening complication was reported without detailed documentation, it was classified as "other."

The annual severe adverse reaction rates were calculated by dividing the number of adverse reactions by the number of patient-years of exposure.

$$\text{Adverse reaction rate} = \frac{\text{Number of adverse reactions}}{\text{Patient-years of exposure}}$$

We were unable to obtain exact calculations on the duration of participation by each patient who did not complete the study. The duration of participation by each patient was not included because these data were not required or collected by the Food and Drug Administration.

The number of patient-years of exposure was therefore estimated by assuming that patients who did not complete each study wore their lenses, on an average, one half the duration of the study. This can be expressed by the following formula:

$$\text{Patient-years of exposure} = \frac{\text{Duration (patients completed)} + \text{Duration (patients enrolled-patients completed)}}{2}$$

A separate analysis using Fisher's exact test ($P \leq .025$) of six-month duration premarket approval studies was performed by comparing each lens group with more than 1,000 patients enrolled that had been investigated using that duration of study (Table 2). Similarly, Fisher's exact test ($P \leq .025$) was performed on two groups (extended-wear soft contact lenses and extended-wear rigid gas-permeable lenses), which had more than 1,000 patients who were studied for 12 months (Table 3).

To determine the effect of study duration on complication rates, the six-, 12-, and 24-month studies of the extended-wear soft contact lens group were compared (Table 4). Fisher's exact test ($P \leq .025$) was used to determine any

TABLE 2
SIX-MONTH STUDIES

CONTACT LENS GROUP	NO. OF PATIENTS ENROLLED	ADVERSE REACTIONS (TOTAL)	CORNEAL ULCERS (TOTAL)	ABRASION/KERATITIS (TOTAL)	ADVERSE REACTION RATE/PATIENT-YEARS (%)	CORNEAL ULCER RATE/PATIENT-YEARS (%)	SEVERE ABRASION/KERATITIS RATE/PATIENT-YEARS (%)
Daily soft	3,591	8	1	4	1/189 (0.0053)	1/1,511 (0.0007)	1/378 (0.0026)
Daily rigid gas permeable	3,907	6	1	3	1/244 (0.0041)	1/1,464 (0.0007)	1/488 (0.0020)
Extended soft*	1,276	7	2	4	1/70 (0.0144)	1/244 (0.0041)	1/122 (0.0082)
Aphakic extended soft†	4,436	59	9	41	1/28 (0.0354)	1/185 (0.0054)	1/41 (0.0246)

*The extended soft group had a significantly higher adverse reaction rate compared to the daily rigid gas-permeable group, $P \leq .025$.

†The aphakic extended soft group had significantly higher rates of adverse reaction and severe abrasion/keratitis when compared to daily soft, daily rigid gas permeable, and extended soft, $P \leq .025$.

TABLE 3
TWELVE-MONTH STUDIES*

CONTACT LENS GROUP	NO. OF PATIENTS ENROLLED	ADVERSE REACTIONS (TOTAL)	CORNEAL ULCERS (TOTAL)	ABRASION/KERATITIS (TOTAL)	ADVERSE REACTION RATE/PATIENT-YEARS (%)	CORNEAL ULCER RATE/PATIENT-YEARS (%)	SEVERE ABRASION/KERATITIS RATE/PATIENT-YEARS (%)
Extended soft	1,989	9	3	4	1/184 (0.0054)	1/522 (0.0018)	1/414 (0.0024)
Extended rigid† gas permeable	1,568	21	3	11	1/60 (0.0167)	1/419 (0.0024)	1/114 (0.0088)

*Note that the adverse reaction, corneal ulcer, and severe abrasion are calculated using patient-years as the denominator. Since the calculation of patient-years factors in discontinued patients, patient complication rates cannot be obtained by simply dividing the number of complications by the total number of patients enrolled.

†The extended rigid gas-permeable group had a significantly higher adverse reaction rate and severe abrasion/keratitis rate compared to the extended soft group, $P \leq .025$.

significance between different duration categories.

Pearson's r correlation was performed between corneal abrasion and keratitis and corneal ulcers in the five groups studied.

Results

The number of patients in the extended-wear rigid gas-permeable lens group (1,568) was smaller than the other lens groups, because these lenses were introduced relatively late in the study (1987; Table 5). The average number of patients enrolled for all studies was 474. The aphakic extended-wear soft contact lens and extended-wear soft contact lens groups each had one study with over 1,100 patients enrolled. The aphakic extended-wear soft contact lens group had one study of 2,728 patients enrolled, which accounted for 60% of the total

aphakic extended-wear soft contact lens population.

There were 22,739 patients enrolled for all 48 studies. Approximately 58% completed the prerequisite study durations. The mean duration of the studies for each group ranged between 4.3 and 13.6 months (Table 6). The extended-wear groups were studied for longer periods (six to 24 months) than the daily-wear groups (4.3 to 6.0 months), because extended-wear lenses were a new modality, and the Food and Drug Administration believed that they warranted more extensive testing than the daily-wear lens regimen.

There were 159 severe adverse reactions reported in the 48 lens studies (Table 1). The most common adverse reaction was corneal abrasion and keratitis, which accounted for 81 of 159 (51%) of all adverse reactions. The next most commonly reported adverse reaction was corneal ulcers, which accounted for 28 of 159 (18%) of all adverse reactions. Severe corneal

TABLE 4
EXTENDED-WEAR SOFT CONTACT LENS STUDIES OF VARYING DURATION

CONTACT LENS GROUP	MONTHS	NO. OF PATIENTS ENROLLED	ADVERSE REACTIONS (TOTAL)	CORNEAL ULCERS (TOTAL)	ABRASION/KERATITIS (TOTAL)	ADVERSE REACTION RATE/PATIENT-YEARS (%)	CORNEAL ULCER RATE/PATIENT-YEARS (%)	SEVERE ABRASION/KERATITIS RATE/PATIENT-YEARS (%)
Extended soft	6	1,276	7	2	4	1/70 (0.0144)	1/244 (0.0041)	1/122 (0.0082)
Extended soft	12	1,989	9	3	4	1/184 (0.0054)	1/522 (0.0018)	1/414 (0.0024)
Extended soft	24	3,499	48	8	14	1/104 (0.0096)	1/627 (0.0016)	1/358 (0.0028)

TABLE 5
TOTAL NUMBER OF PATIENTS ENROLLED IN
PREMARKET APPROVAL STUDIES AND PATIENT
COMPLETION RATES FOR CONTACT LENS WEARING
GROUPS

CONTACT LENS GROUP	NO. OF STUDIES*	PATIENTS ENROLLED	COMPLETION RATE (COMPLETED/ENROLLED) (%)
Daily soft	19	5,635	66
Daily rigid gas permeable	8	3,907	65
Extended soft	11	6,764	52
Extended rigid gas permeable	5	1,568	60
Aphakic extended soft	5	4,865	49
Total	48	22,739	58

*Average number of patients for all studies is 474.

vascularization (eight of 159 [5.0%]), corneal infiltrates (seven of 159 [4.4%]), and severe corneal edema (six of 159 [3.8%]) were less frequent. Severe uveitis and iritis (two of 159 [1.3%]) and severe pannus (two of 159 [1.3%]) were the least reported adverse reactions.

There were 14 adverse reactions, including two corneal ulcers, in the cosmetic daily-wear lens groups (9,542 patients) and 85 adverse reactions, including 16 corneal ulcers, in the extended-wear cosmetic groups (8,332 patients). Since the greater number of complications in the extended-wear contact lens group may have been because of the longer period of observation compared to the daily-wear group, we computed the corneal ulcer and adverse reaction rates per patient-year of observation to provide overall estimates of relative risks (Table 7). The annual incidence of severe adverse reactions was lowest in the daily-wear soft contact lens (0.00416) and the daily-wear rigid gas-permeable lens (0.00410) groups. The extended-wear soft and extended-wear rigid gas-permeable contact lenses had intermediate rates of severe adverse reactions (0.00894 and 0.0167, respectively), whereas the aphakic extended-wear soft contact lens group had the highest rate (0.0299) of severe adverse reactions. Similar group trends were noted when the incidence of corneal ulcers and corneal abrasion and keratitis were determined (Table 7). There was a strong correlation between corneal abrasion and keratitis and corneal ulcers in the five groups studied ($r = .973$, $P < .01$).

Comparison of groups studied for six-month duration (Table 2) disclosed a significantly higher adverse reaction rate, including severe abrasion and keratitis, in the aphakic group when compared to daily-wear soft, daily-wear rigid gas-permeable, and extended-wear soft contact lens groups ($P \leq .025$). The cosmetic extended-wear soft contact lens group had a higher adverse reaction rate, which was significantly different when compared to the daily-wear rigid gas-permeable lens users ($P \leq .025$) and approached a significant difference when compared to daily-wear soft lens users ($P = .0485$). Analysis of 12-month studies (Table 3) disclosed a significantly higher rate of adverse reactions and severe abrasion and keratitis in the extended-wear rigid gas-permeable group when compared to extended-wear soft lens rates ($P \leq .025$).

There was no significant difference in adverse reaction, corneal ulcer, and severe abrasion and keratitis rates between the six-, 12-, and 24-month studies in the extended-wear soft contact lens group (Table 4).

Discussion

The incidence of corneal ulcers was one in 1,923 patient-years in the daily-wear soft contact lens group and one in 1,471 patient-years in the daily-wear rigid gas-permeable group (Table 7). Although not directly comparable, these are consistent with the previous reports in daily-wear soft lens users.^{3,4} In a study of 66,000 patients followed up for one year, it was noted that the corneal ulcer rates were 3.2 and

TABLE 6
FOOD AND DRUG ADMINISTRATION PREMARKET
APPROVAL STUDIES*

CONTACT LENS GROUP	DURATION OF STUDY		NO. OF STUDIES
	MEAN (MOS)	RANGE (MOS)	
Daily soft	4.3	3 to 6	19
Daily rigid gas permeable	6.0	6	8
Extended soft	13.6	6 to 24	11
Extended rigid gas permeable	12.0	12	5
Aphakic extended soft	8.0	6 to 12	5

*Average number of patients for all studies is 474.

TABLE 7
OVERALL ANNUAL CORNEAL ULCER AND SEVERE ADVERSE REACTION RATES

CONTACT LENS GROUP	NO. OF PATIENTS	ADVERSE REACTION RATE/ PATIENT-YEARS (%)	CORNEAL ULCER RATE/ PATIENT-YEARS (%)	SEVERE ABRASION/KERATITIS RATE/ PATIENT-YEARS (%)*
Daily soft	5,635	1/240 (0.00416)	1/1,923 (0.00052)	1/480 (0.00208)
Daily rigid gas permeable	3,907	1/244 (0.0041)	1/1,471 (0.00068)	1/488 (0.00205)
Extended soft	6,764	1/112 (0.00894)	1/549 (0.00182)	1/326 (0.00307)
Extended rigid gas permeable	1,568	1/60 (0.0167)	1/418 (0.00239)	1/114 (0.00875)
Aphakic extended soft	4,865	1/33 (0.0299)	1/201 (0.00498)	1/49 (0.0204)

*The correlation between corneal ulcer and severe abrasion/keratitis is $r = .973$, $P \leq .01$.

3.0 per 10,000 patient-years for daily-wear soft and rigid gas-permeable lens wearers, respectively.⁴ Another study estimated severe microbial keratitis rates of two in 15,000 extended-wear soft contact lens patients based on after hours and emergency visits noted at a large referral center over a two-year period.³ Poggio and associates¹ noted an incidence of ulcerative keratitis in five New England states of 4.1 per 10,000 for daily-wear soft and 20.9 per 10,000 for cosmetic extended-wear lenses. In a case control study, Schein and associates⁵ noted that the risk of developing ulcerative keratitis was ten to 15 times greater in cosmetic extended-wear users who wore their lenses overnight when compared to cosmetic daily-wear users who did not wear lenses overnight.⁵ Our study is unique, however, since the patients were closely monitored throughout the entire study period. Since patients were aware of their participation in an investigational study, were asked to report any untoward reactions immediately, and were also closely monitored, the severity of adverse reactions may be less than in noninvestigational populations.

Within groups, there was no apparent trend toward disproportionate clustering of complications within premarket approval studies with the exception of the aphakic extended-wear population. One study of aphakic lenses accounted for 21 of 60 (35%) of all adverse reactions and 15 of 40 (37%) severe abrasion and keratitis cases in the entire aphakic extended-wear contact lens group but made up only 726 of 2,728 (37%) of the aphakic extended-wear

study population. A second aphakic extended-wear soft contact lens study had 2,728 patients, which accounted for 2,728 of 4,865 patients (56%) who were enrolled in all of the aphakic extended-wear soft contact lens groups. The adverse reaction rate for their group (34 of 60 [57%]) was similar to that of the entire aphakic group; however, this study accounted for nine of ten of all corneal ulcers in the aphakic extended-wear soft contact lens group. The nonaphakic groups demonstrated no disproportionate clustering of complications within groups.

We estimated complication rates for cosmetic daily- and extended-wear groups because the cosmetic daily- and extended-wear investigations had different durations of study (Table 7). The daily-wear studies tended to be of shorter duration (4.3 to 6.0 months) than the extended-wear studies (6.0 to 13.6 months). For this reason, these different groups could not be compared in a statistical fashion.

In groups studied for an equivalent duration (six months), a significantly increased risk (6.7 times) of severe adverse reaction was demonstrated in the aphakic extended-wear soft group compared to the daily-wear soft contact lens group (Table 2). Cosmetic extended-wear soft contact lenses demonstrated an increased risk (3.5 times) of developing a severe adverse reaction, which was significantly different ($P \leq .025$) when compared to the daily-wear rigid gas-permeable group. A similar trend of increased risk (2.7 times) was noted in the cosmetic extended-wear soft group when com-

pared to the daily-wear soft contact lens group for a six-month period. This comparison approached significance ($P = .0485$).

There were three reports of corneal ulcers in 1,568 patients enrolled in the extended-wear rigid gas-permeable group. The number of corneal ulcers noted in this group was too small to establish a trend; however, there were a total of 21 adverse reactions in this same group (a reaction rate of one per 60 patient-years). This rate was significantly higher than the extended-wear soft contact lens adverse reaction rate (one per 184 patient-years, Table 3 [$P \leq .025$]), which raises concern regarding the extended-wear rigid gas-permeable group, especially since both studies had the same duration (12 months). It may be that the extended-wear rigid gas-permeable adverse reaction rates were higher because of recent introduction of this modality to practitioners. As more studies are performed and more oxygen-permeable materials are introduced, these rates may decrease. This rate was higher than we anticipated, which stresses the need for studying large groups of patients (1,000 to 4,000) over longer periods (one year).

Comparisons of extended-wear soft cosmetic contact lens groups for varying durations of study disclosed no trend toward increased rates of adverse reactions with different durations of study (Table 4). This analysis demonstrates that study duration does not have a strong effect on the relative frequency of severe adverse reactions in the extended-wear soft contact lens group.

The overall rate of corneal ulcer formation in the cosmetic extended-wear soft contact lens group was 3.5 times greater than the daily-wear soft contact lens group (Table 8). This increased rate is consistent with the 4.4-fold increase in case reports of extended-wear corneal ulcers in

soft lens wearers when compared to daily lens wearers if a number of studies are combined and the market share is considered.^{6,7}

Patient completion rates were lower in the extended-wear soft contact lens and aphakic extended-wear soft contact lens groups, which may be expected since these studies were performed over longer periods compared to the daily-wear studies (Tables 5 and 6). Aphakic extended-wear soft contact lens users had the lowest completion rates, possibly because the study duration may be longer, but more importantly those patients are older, have had previous operations, and have more lens care difficulties.⁸

Previous studies in aphakic extended-wear soft contact lens wearers have demonstrated the rates of corneal ulcer formation to vary between 0% and 7%, with most studies reporting a 2% to 7% rate of corneal ulcers.⁹⁻¹³ The lower rates (0.5% per patient-year) of corneal ulcers noted in our study may be because of the close follow-up patients received as a part of an investigational study. Moreover, these patients appear to be at greater risk of developing a serious, sight-threatening complication. Aphakic extended-wear soft contact lenses in selected patients, however, represent an important therapeutic option. These patients should be warned that they are at higher risk of developing a serious, sight-threatening complication and that if their eye becomes red or irritated, the lens should be promptly removed, and they should seek professional care.

Corneal abrasion and keratitis were the most common adverse reaction in this study, which accounted for 81 of 159 (51%) of all adverse reactions. Corneal ulcer was the second most common adverse reaction (28 of 159 [18%]), and this complication tended to occur more often in the groups that had more frequent reports of corneal abrasion and keratitis. This raises concern as to whether contact lens wearing groups that have frequent abrasion and keratitis episodes may be exposed to developing corneal ulcers. Clinical and laboratory experiences indicate that a break in the corneal epithelium (corneal abrasion and keratitis) may predispose the cornea to the development of corneal ulcers¹⁴⁻²²; however, it is difficult to draw a direct association between corneal abrasion and keratitis and corneal ulcers. These findings strengthen the guidelines that patients remove their lenses if their eyes become red or irritated to minimize severe corneal abrasion.²³

TABLE 8
RATIO COMPARISON OF CONTACT LENS GROUPS

CONTACT LENS GROUPS	CORNEAL ULCER	ADVERSE REACTION	KERATITIS/ ABRASION
Daily soft/daily rigid	0.77	1.01	1.00
Extended soft/daily soft	3.50	2.20	1.50
Extended rigid/daily rigid	3.50	4.10	4.30
Aphakic extended/daily soft	9.60	7.20	9.80
Extended soft/extended rigid	0.76	0.54	0.35
Aphakic extended/extended soft	2.70	3.30	6.60

Our format for data reporting did not allow evaluation of the relation between adverse reactions (including corneal ulcers) and duration of lens wear, frequency of lens replacement or removal, frequency of disinfection, recent lens manipulations, degree of lens deposit formation, improper lens hygiene, and other possible risk factors. Previous reports on daily-wear soft contact lens users who develop corneal ulcers have noted inappropriate overnight wear, frequent contamination of lens cases, and improper or no disinfection as factors contributing to ulcer formation.^{1,5,13,24,25} The use of salt tablets, distilled water, and homemade saline may also result in bacterial or *Acanthamoeba* keratitis.^{14,26,27}

Patients who wore lenses on an extended-wear basis generally wore them on an overnight basis up to 30 days. Manufacturers generally encouraged fitters to instruct that the lenses be worn overnight in their studies up to 30 days. Patients who use extended-wear lenses were not encouraged to wear their lenses on a daily basis, since this would not provide information on the safety of extended (overnight) wear.

Based on more recent studies,^{1,5} the Food and Drug Administration has requested the manufacturers of cosmetic extended-wear soft contact lenses to recommend a wearing time of one to seven days in the product labeling (written communication, U.S. Department of Health and Human Services, John Villforth, Public Health Service, Food and Drug Administration Center for Devices and Radiologic Health, HFZ-250, Rockville, Maryland, May 30, 1989). This recommendation for patients to reduce dramatically the frequency of overnight wear is reasonable given the increased risk of serious, sight-threatening complications associated with overnight lens wear.

References

1. Poggio, E. C., Glynn, R. J., Schein, O. D., Seddon, J. M., Shannon, M. J., Scardino, V. A., and Kenyon, K. R.: The incidence of ulcerative keratitis among users of daily-wear and extended-wear soft contact lenses. *N. Engl. J. Med.* 321:779, 1989.
2. Smith, R. E., and MacRae, S. M.: Contact lenses. Convenience and complications. *N. Engl. J. Med.* 321:824, 1989.
3. Chalupa, E., Swarbrick, H. A., Holden, B. A., and Sjöstrand, J.: Severe corneal infections associated with contact lens wear. *Ophthalmology* 94:17, 1987.
4. Hamano, H., Kitano, J., Mitsunaga, S., Kojima, S., and Kissling, G. E.: Adverse effects of contact lens wear in a large Japanese population. *CLAO J.* 11:141, 1985.
5. Schein, O. D., Glynn, R. J., Poggio, E. C., Seddon, J. M., Kenyon, K. R., and the Microbial Keratitis Study Group: The relative risk of ulcerative keratitis among users of daily-wear and extended-wear soft contact lenses. *N. Engl. J. Med.* 321:773, 1989.
6. MacRae, S. M.: Epidemiologic aspects of contact lens associated infections from the cornea. In Cavanaugh, D. H. (ed.): *The Cornea*. Transactions of the World Congress on the Cornea. New York, Raven Press, 1988, pp. 289-292.
7. Herman, C. L.: An FDA survey of U.S. contact lens wearers. *Contact Lens Spectrum* 7:89, 1987.
8. Lemp, M. A., Blackman, H. J., Wilson, L. A., and Levill, A. S.: Gram negative corneal ulcers in elderly aphakic eyes in extended-wear lenses. *Ophthalmology* 91:60, 1984.
9. Spoor, T. C., Hartel, W. C., Wynn, P., and Spoor, D. K.: Complications of continuous-wear soft contact lenses in a non-referral population. *Arch. Ophthalmol.* 102:1312, 1984.
10. Patrinely, J. R., Wilhelmus, K. R., Rubin, J. M., and Key, J. E.: Bacterial keratitis associated with extended wear soft contact lenses. *CLAO J.* 11:234, 1985.
11. Eichenbaum, J. W., Feldstein, M., and Podos, S. M.: Extended wear aphakic soft contact lenses and corneal ulcers. *Br. J. Ophthalmol.* 66:663, 1982.
12. Schonder, A. A., Conkin, R. R., and Ageline, E. A.: Clinical evaluation of extended-wear lidofilcon and contact lens in aphakia. *Ann. Ophthalmol.* 14:935, 1982.
13. Martin, N. F., Kracher, G. P., Stark, W. J., and Maumenee, A. E.: Extended wear soft contact lenses for aphakic correction. *Arch. Ophthalmol.* 101:39, 1983.
14. Wilson, L. A., Schlitzer, R. L., and Ahearn, D. G.: *Pseudomonas* corneal ulcers associated with soft contact lens wear. *Am. J. Ophthalmol.* 92:546, 1981.
15. Hazlett, L. D., Wells, P. A., and Berk, R. S.: The mouse cornea as a model for *Pseudomonas* infections. Further studies on penetrating and lysis of the unwounded eye. In Hollyfield, J. G. (ed.): *The Structure of the Eye*. New York, Elsevier/North Holland Publishing Co., 1982, pp. 279-296.
16. ———: Scanning electron microscopy of the normal and experimentally infected ocular surface. *Scan. Electron Microsc.* 3:1379, 1984.
17. Ramphal, R., McNiece, M. T., and Polack, F. A.: Adherence of *Pseudomonas aeruginosa* to the mouse cornea. A step in pathogenesis of corneal infections. *Ann. Ophthalmol.* 13:421, 1981.

18. Hyndiuk, R. A.: Experimental *Pseudomonas* keratitis. Trans. Am. Ophthalmol. Soc. 79:541, 1981.
19. Stern, G. A., Weitzenkorn, D., and Valenti, J.: Adherence of *Pseudomonas aeruginosa* to the mouse cornea. Epithelial versus stromal adherence. Arch. Ophthalmol. 100:1956, 1982.
20. Stern, G. A., Lubeniwski, A., and Allen, C.: The interaction between *Pseudomonas aeruginosa* and the corneal epithelium. Arch. Ophthalmol. 103:1221, 1985.
21. Stern, G. A.: Pathogenesis of contact lens associated *Pseudomonas* corneal ulceration. In Cavanaugh, D. H. (ed.): The Cornea. Transactions of the World Congress on the Cornea. New York, Raven Press, 1988, pp. 309-311.
22. Baum, J., and Panjwani, N.: Adherence of *Pseudomonas* to soft contact lenses and cornea mechanisms and prophylaxis. In Cavanaugh, D. H. (ed.): The Cornea. Transactions of the World Congress on the Cornea. New York, Raven Press, 1988, pp. 301-307.
23. MacRae, S. M., Cohen, E. J., and Andre, M.: Guidelines for safe contact lens wear. Am. J. Ophthalmol. 103:832, 1987.
24. Donnenfeld, E. D., Cohen, E. J., Arentsen, J. J., Genvert, G. I., and Laibson, P. R.: Changing trends in contact lens associated corneal ulcers. An overview of 116 cases. CLAO J. 12:145, 1986.
25. Mondino, B. J., Weissman, B. A., Farb, M. D., and Pettit, T. H.: Corneal ulcers associated with daily-wear and extended-wear contact lenses. Am. J. Ophthalmol. 102:58, 1986.
26. *Acanthamoeba* keratitis associated with contact lenses. M.M.W.R. 35:405, 1986.
27. Stehr-Green, J. K., Bailey, T. M., Brandt, F. H., Carr, J. H., Bond, W. W., and Visvesvara, G. S.: *Acanthamoeba* keratitis in soft contact lens wearers. A case control study. JAMA 57:258, 1987.

OPHTHALMIC MINIATURE

Broadminded, master of English style as well as the subject with which his journal deals; and, in addition, full of human kindness, a sense of humor, and a clear understanding of each of his writers' special gifts and aptitudes and the way in which to encourage and develop all these to the greatest possible extent.

How spontaneously and even joyously an author writes for such an editor! He will almost work himself to death for him.

Such an editor may well be termed "a Doctor Casey A. Wood."

T. H. Shastid, *Tramping to Failure*
Ann Arbor, George Wahr, 1937

Infectious Keratitis and Cyanoacrylate Adhesive

Timothy B. Cavanaugh, M.D., and John D. Gottsch, M.D.

We studied three patients with infectious keratitis that occurred after cyanoacrylate gluing despite prophylactic antibiotic therapy. Two patients developed culture-positive bacterial ulcers, one caused by a methicillin-resistant *Staphylococcus aureus* and the other by *Haemophilus influenzae*. The third patient developed a fungal keratitis. Two patients required penetrating keratoplasty. Each infection and perforation was concealed by the opaqueness of the glue. The pain of the infectious ulcers may have been obscured by the ocular surface irritation and drying induced by glue. Tissue toxicity, microbial colonization, use of bandage lenses, and long-term broad-spectrum antibiotics may precipitate glue-related corneal infections. Masking of underlying infection and the development of resistant organisms should be considered when using this mode of therapy.

CYANOACRYLATE ADHESIVE was introduced by Coover and associates¹ in 1959. This adhesive has the unique property of being rapidly converted from a liquid to a solid state by anionic polymerization that occurs at room temperature without the need for catalysts, solvents, or application of pressure.

The first clinical reports on cyanoacrylates are from vascular surgeons.^{2,3} In 1963, Ellis and Levine⁴ described sutureless ocular surgery on a myriad of ocular structures in rabbits by using Eastman 910 monomer or methyl-2-cyanoacrylate. Since these early studies, applications for this versatile material have been reported,⁵ mostly using the higher analogues. Corneal uses of tissue adhesive include sealing of perforations,⁶ artificial epithelium or epikeratopro-

thesis, artificial endothelium,^{7,8} inhibition of ongoing stromal melting, and prevention of noninfectious stromal ulceration.⁹

Glue has been successfully used in the treatment of both infectious and noninfectious ulcerations. If properly applied, tissue adhesive can remain in place for weeks, which allows healing to occur in the underlying stroma. Cyanoacrylates have been shown to inhibit leukocytes and to possess bactericidal properties. This proposed antibacterial effect may provide a false sense of security for ophthalmologists who use glue in their practices. We studied three patients with infectious keratitis that was masked by cyanoacrylate adhesives.

Case Reports

Case 1

A 60-year-old woman undergoing dialysis secondary to diabetic renal failure initially had filamentary keratitis and a shallow corneal ulcer without stromal infiltrate or hypopyon. Despite treatment with topical tobramycin, the ulcer enlarged and was accompanied by a significant hypopyon within three weeks. Cultures were positive for *Streptococcus viridans* and coagulase-negative *Staphylococcus aureus*. Treatment was begun with fortified topical cefazolin and gentamicin sulfate along with systemic corticosteroids and tetracycline. The ulcer was sterilized, but an epithelial defect and ulcer persisted for the next 3½ months despite patching, bandage contact lenses, and collagen shields. Final healing was accompanied by diffuse corneal edema and bullous keratopathy. She was referred to our institution three months later with a recurrent corneal ulcer for which she received fortified topical cefazolin and tobramycin. Cultures were negative, whereas smears disclosed inflammatory cells but no organisms. Topical prednisolone acetate was started and a rheumatologic examination ordered. The rheumatoid arthritis latex agglutinin test was positive at a dilution of 1:20; however, the remainder of the blood tests were

Accepted for publication Jan. 17, 1991.

From the Cornea Service, Wilmer Ophthalmological Institute, Johns Hopkins University School of Medicine, Baltimore, Maryland. This study was presented in part at the Ocular Microbiology and Immunology Group meeting, Atlanta, Georgia, Oct. 27, 1990.

Reprint requests to John Gottsch, M.D., Maumenee Rm. 313, 600 N. Wolfe St., Baltimore, MD 21205.

negative. The ulcer slowly progressed to a descemetocele, which was treated with butylcyanoacrylate and a bandage contact lens. Informed consent was obtained from the patient. The fortified antibiotics were tapered, and antibiotic coverage was provided by polymyxin B and trimethoprim. Within two weeks, the patient had pain and a hypopyon. Removal of the adhesive disclosed an ulcer and central perforation (Fig. 1). An emergent penetrating keratoplasty was performed. Cultures were positive for heavy growth of methicillin-resistant *S. aureus*, which was sensitive to vancomycin and tetracycline. She was treated with vancomycin eyedrops as well as tetracycline ointment postoperatively.

Case 2

An 18-year-old woman with atopy and gammaglobulin deficiency had a two-month history of decreased vision, tearing, and photophobia. Examination disclosed a diffuse punctate epitheliopathy with a central stromal melt and 75% thinning. All cultures and immunologic blood studies were negative. The patient was given topical prednisolone acetate, but the corneal melt proceeded to perforation one month later. The patient was hospitalized and treated with systemic antibiotics. Informed consent was obtained, and the perforation was sealed with butylcyanoacrylate adhesive and a bandage contact lens. Repeat cultures were negative. Prednisolone acetate was continued along with topical gentamicin sulfate. Three weeks later, the eye developed a recurrent melt and perforation that required readmission and repeat glue therapy. A corneal biopsy (Fig. 2) was performed, and transmission electron microscopy showed intracytoplasmic inclusions in



Fig. 1 (Cavanaugh and Gottsch). Case 1. Central perforated infectious ulcer after glue removal.

keratocytes consistent with *Paramyxovirus* species. The eye continued to melt around the adherent glue patch; thus, an urgent penetrating keratoplasty was performed. Removal of the adhesive at the time of surgery disclosed an extensive 7.0-mm corneal melt with underlying necrotic iris and lens material. Xanthochromic liquid percolated from the posterior segment, but there was no frank purulence. Cultures demonstrated heavy growth of *Haemophilus influenzae*. The organism was sensitive to ampicillin, cefoxitin, chloramphenicol, and tetracycline. The endophthalmitis was treated by vitrectomy, intravitreal antibiotics, intravenous ampicillin, and topical chloramphenicol.

Case 3

A healthy 5-year-old boy received a penetrating injury from a nail to his right eye. The corneal laceration was repaired surgically at another hospital. Three days later the patient was referred to us with a flat anterior chamber and a wound leak (Fig. 3). The patient was admitted and, with parental consent, underwent lensectomy and corneal laceration repair, which required butylcyanoacrylate application. A bandage contact lens was not placed because of extensive conjunctival chemosis. He was treated postoperatively with fortified topical cefazolin and gentamicin sulfate along with a three-day intravenous course of the same. One week later, a therapeutic contact lens was fit over a tightly adherent glue patch. Six weeks later the patient underwent an anterior vitrectomy, posterior capsulotomy, and revision of the corneal laceration. The glue was removed, which concealed some broken sutures but no leak. A small amount of adhesive was added nasally to provide adequate wound closure and reinforcement. Full-time patching and amblyopia therapy was instituted. Two weeks later he came to the emergency room with pain and purulent drainage for two days. A corneal ulcer was found under the glue that was culture-positive for *Aspergillus fumigatus*. Therapy with oral ketoconazole and topical natamycin was begun. The ulcer slowly healed to allow visual acuity of 20/40 with a gas-permeable contact lens on last examination (Fig. 3).

Discussion

In each of the above cases, the diagnosis of infectious keratitis was concealed by the

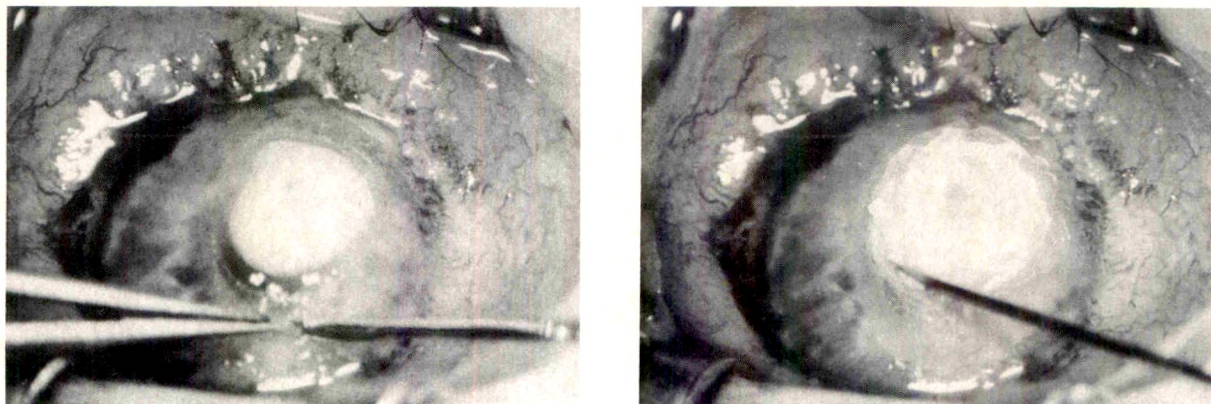


Fig. 2 (Cavanaugh and Gottsch). Case 2. Left, Corneal biopsy in area of leakage around glue. Right, Application of additional adhesive to seal the perforation.

opaqueness of the polymerized adhesive. Cyanoacrylates are colorless, clear liquids as monomers but become chalky white solids within ten to 20 seconds upon polymerization. If a liberal amount of adhesive is used so that it covers the cornea, it will not only impair the patient's vision but will markedly limit the clinician's view of underlying tissues. Only our first case provided a visible clue to infection in the form of a hypopyon that could be seen around the lower edges of the adhesive.

Most infectious ulcers have associated pain that often prompts the patient to seek medical care. It is well known that application of tissue adhesive induces a range of discomfort. Great care must be taken to avoid rough edges on the glue surface to prevent a severe foreign body sensation and inflammatory response in the eyelids. There is also a significant degree of localized corneal dehydration adjacent to the glue that can produce discomfort even with a bandage contact lens. Patients are told to expect soreness after glue placement so they get accustomed to some degree of pain. Any additional discomfort incited by an ulcer can be either masked by that already present or is simply passed off as expected. Both can lower a patient's level of concern and delay the diagnosis and subsequent treatment of a potentially devastating condition.

Aside from the adhesive itself, four additional risk factors must be considered in these patients. Previous microbial colonization of the presumably sterilized corneas provides an avenue for the establishment of infection after glue placement. The increased infection risk associated with the use of soft contact lenses is well documented and cannot be overlooked in the evaluation of these cases. Immunosuppression may have played a role in the development of

infectious keratitis in two of the three patients. Finally, the use of long-term broad-spectrum antibiotics may have selected for some resistant or unusual microbes.

Direct irritation induced by the rough glue surface can generate sufficient trauma to the ocular surface to provoke a mechanical keratoconjunctivitis leading to epithelial breakdown and infectious keratitis. Gasset and associates¹⁰ found that solid flakes of polymerized adhesive were released into the conjunctival sac that abraded the corneal and conjunctival surfaces. Mechanical trauma can be minimized by proper application of the adhesive and by a precisely fit bandage contact lens.

Direct tissue toxicity and necrosis can compromise the host's immune barriers and greatly enhance the propensity for the development of infection. The histotoxicity of cyanoacrylates is well documented and appears to be inherent in the chemical makeup of the material or in its byproducts. Unreacted monomer can become trapped in the polymerized adhesive and diffuse slowly into tissues. Monomer impurities are incorporated into the material to act as preservatives and can also leak into tissues.¹¹ The fully polymerized form appears to behave like an inert foreign body. Polymer degradation products are important toxins.

Aronson and associates¹² divided the corneal inflammatory response to glue histologically into two stages. The acute reaction is triggered by protein binding, complement fixation, and polymorphonuclear chemotaxis and activation. The late response is granulomatous and directed toward a particulate stimulus. It has been demonstrated in rats that the shorter chain homologues, such as methyl, tend to produce acute reactions that can be intensely necrotizing and pyogenic. Conversely, the longer chain,

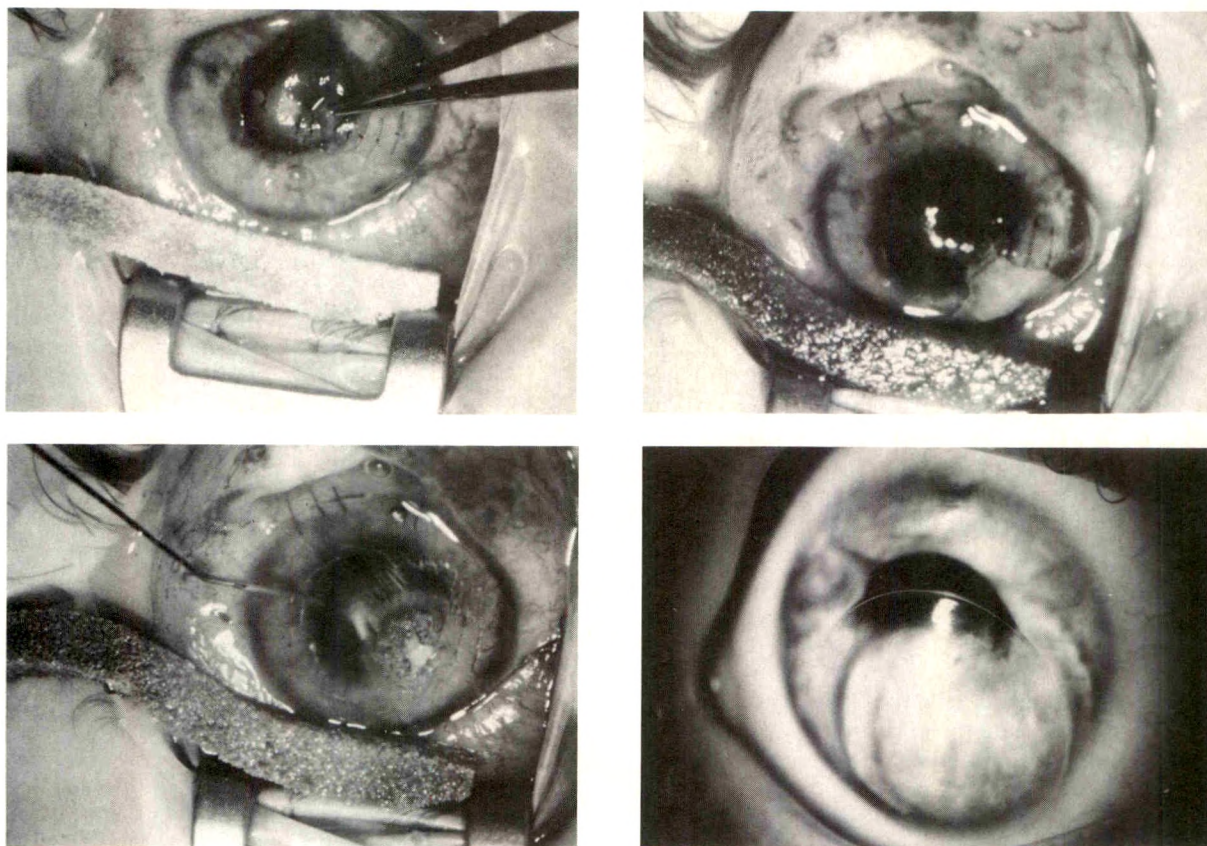


Fig. 3 (Cavanaugh and Gottsch). Case 3. Top left, Unopposed jagged edge of corneal laceration. Top right, Persistent leakage from perforation with positive Seidel's sign. Bottom left, Sealed perforation after application of cyanoacrylate. Bottom right, Corneal scar covered by contact lens after healing of fungal keratitis.

higher molecular weight homologues elicited transient inflammation followed by a foreign body granuloma response.¹³

Refojo, Dohlman, and Koliopoulos¹⁴ provided a comprehensive review of cyanoacrylates in 1971 that included data on toxicity. They stated that "the toxic effects of synthetic polymers on tissues are related in part to their breakdown products and to the rate at which they are released." The mechanism of aqueous cyanoacrylate degradation involves cleavage of carbon to carbon bonds to release formaldehyde and cyanoacrylate. Cellular damage will occur until local detoxification of these substances occurs. The degradation rate is a function of the particle size of the polymer.^{15,16} The methyl derivative degrades rapidly and is known to be toxic, whereas longer carbon chain derivatives degrade slowly and generate a much less noxious stimulus.¹⁷ The tolerance levels of the 2-cyanoacrylate adhesives have been classified in the following order from best to least tolerated: n-decyl, n-octyl, n-heptyl, n-hexyl, n-butyl, isobutyl, trifluoroisopropyl, and methyl.¹⁸

Numerous researchers have demonstrated that the toxicity of tissue adhesive is directly proportional to dose.¹⁹ Fortunately, the amounts required for ocular procedures are exceedingly modest.

Many investigators have reported that cyanoacrylates have a self-sterilizing or bactericidal property. At least as many have put forth evidence to the contrary disclosing contamination and bacterial growth in glue.

As early as 1961, Fassett and associates²⁰ demonstrated that several bacteria including *Escherichia coli* and *S. aureus* were not capable of surviving in the polymer. Plastic surgery incisions closed with tissue adhesive have been shown to be protected against experimentally induced wound infection with *S. aureus*.²¹ *Neisseria catarrhalis*, *Gaffky* species, and *S. aureus* have been reported to be inhibited to varying degrees by the application of isobutyl-cyanoacrylate. Complete destruction of actively growing colonies occurred only with alpha-hemolytic *Streptococcus* species. From the appearance of the zones of inhibition, Jandinski and Sonis²²

hypothesized that a diffusible bacteriostatic substance was present in the polymer. This substance may be the breakdown products of depolymerization such as formaldehyde and cyanoacetate. Rietveld, Garnaat, and Seutter-Berlage²³ observed both bacterial toxicity and mutagenicity toward *Salmonella typhimurium* with the methyl 2-cyanoacrylate monomer but none with the ethyl, n-butyl, or isobutyl groups. This evidence parallels the host toxicity studies in which the lower homologues were more destructive. In a similar experiment, Leyman, West, and Leonard²⁴ evaluated the effect of nine different alkyl 2-cyanoacrylates on the growth of *E. coli* and *S. aureus* in culture. Just as the histotoxicity of each material had previously been shown to be a function of its rate of degradation, the relative bacterial inhibition induced by each homologue was predictable based on its degradation rate. The adhesives were increasingly more bacteriotoxic with decreasing chain length and increasing breakdown rates.

Although there is considerable research supporting an antibacterial property to cyanoacrylates, greater evidence to the contrary exists. Leyman, West, and Leonard²⁴ did recover viable bacteria from the polymerized glue surface after removal from bacterial plates. Similarly, Page and Borick²⁵ recovered viable bacterial spores in methyl cyanoacrylate monomer for up to 14 days. Both of these studies suggest that adhesive may act as a vehicle for bacteria if the monomer was contaminated before use. Matsumoto and associates²⁶ compared the effects of glue versus antibiotics on six different bacteria. Cyanoacrylates were found to be inferior to oxytetracycline, penicillin, kanamycin sulfate, and chloramphenicol in bacterial inhibition. Their studies concluded that methyl, isobutyl, and n-butyl cyanoacrylates were neither bactericidal nor bacteriostatic for either vegetative or spore forms of *S. epidermidis*, *S. aureus*, lactose fermenting enterobacteria, *Pseudomonas aeruginosa*, *Clostridium* species, and group D *Streptococcus*.²⁶ Butyl 2-cyanoacrylate has been shown to be completely ineffective against gram-negative microorganisms but exhibits some bactericidal activity against gram-positive bacteria. This activity diminished after 30 minutes, which suggests that there is no long-term antibacterial effect. The discordance in inhibition is probably based on the differences between the bacterial cell walls of the two types of organisms. The active double bond in the monomer can combine with free amino or hy-

droxyl groups in the cell wall of gram-positive bacteria. The lipopolysaccharide capsule surrounding the cell wall in gram-negative organisms can act as a barrier to glue binding.²⁷

The physical nature of the polymerized adhesive may predispose it to bacterial colonization. Materials with irregular surfaces allow bacteria to gather in cavities and subsequently to colonize the entire surface. Coagulase-negative staphylococci are the most common organisms infecting implanted biomaterials.²⁸ Olson, Ruseska, and Costerton²⁹ studied the adherence and colonization of *S. epidermidis* to the surface of n-butyl 2-cyanoacrylate by scanning electron microscopy. A viable, dividing bacterial biofilm rapidly covered the glue surface, which led them to conclude that cyanoacrylate is not bactericidal.

The addition of substances to cyanoacrylate to reduce its toxicity or to enhance antibacterial properties has been suggested. Early reports showed that adhesives exhibited toxicity in tissues through thrombosis and necrosis.³⁰ Papa-theofanis³¹ noted these findings and proposed that glue toxicity may be mediated by thromboxanes and prostaglandins as their release can impair blood flow causing the thrombosis that leads to ischemia and tissue necrosis. His study evaluated the effect of prostaglandin H synthase inhibitors and of other mediators of inflammation on glue-induced tissue damage. The addition of both acetylsalicylic acid and indomethacin to a cell suspension containing cyanoacrylate yielded significantly better cell viability. Pretreatment with superoxide dismutase led to enhanced numbers of viable cells, whereas the use of catalase did not. Finally, scavenging lipid hydroperoxidases with glutathione peroxidase and reduced glutathione lessened resultant cytotoxicity. Their proposed mechanism involves cyanoacrylates generating lipid hydroperoxidases that, in turn, activate prostaglandin and thromboxane synthesis leading to cell membrane oxidation and lysis. It is suggested that concomitant treatment with antioxidants and antiinflammatory agents may reduce or prevent the tissue damage that invariably accompanies cyanoacrylate use.³¹

The addition of antibiotics to biomaterials can reduce the risk of infection related to the presence of a foreign body and can provide a vehicle for the slow release of antibiotic.³² Olson, Ruseska, and Costerton²⁹ suggested the incorporation of an antibiotic in the cyanoacrylate monomer to create a bacteria-resistant polymer. Shenk and associates³³ studied the

ability of n-butyl-2-cyanoacrylate to act as a vehicle for local delivery of antibiotics to vascular grafts infected by *E. coli* and *S. aureus* in dogs. Tobramycin powder was mixed with the adhesive monomer, and the suspension was used to seal graft sites. Nearly all of the control group had positive cultures, whereas the cultures of the treatment group were all negative. This research suggests that the addition of tobramycin to cyanoacrylate monomer can be effective in the treatment and prevention of infection.

Clinicians should be aware of the potential for development of microbial infections after applying glue. Closer follow-up of immunosuppressed patients is suggested. Resistant organisms should be suspected if an infection develops during long-term treatment with prophylactic broad-spectrum antibiotics. Glue should be removed upon suspicion of any underlying abnormalities to obtain an adequate examination and prevent a delay in diagnosis. Predisposition to corneal infection can be minimized by reducing tissue toxicity through the use of additive-free higher chain homologues and smaller amounts. Finally, the admixture of injectable antibiotics with liquid cyanoacrylate monomer may allow the polymerized adhesive to act as a reservoir for the slow release of antimicrobial agents. Further studies evaluating antibiotic release from glue and local tissue levels need to be conducted before this is proven as an effective method of drug delivery. With proper use, adhesive can remain a valuable adjunctive therapy for the treatment of corneal ulcers, perforations, and stromal thinning disorders.

References

1. Coover, H. W., Jr., Joyner, F. B., Shearer, N. H., Jr., and Wicker, T. H., Jr.: Chemistry and performance of cyanoacrylate adhesives. S.P.E. Tech. Papers 5:92, 1959.
2. Nathan, H. S., Nachlas, M. M., Solomon, R. D., Halpern, D. B., and Seligman, A. M.: Nonsuture closure of arterial incisions by a rapidly polymerizing adhesive. *Ann. Surg.* 152:648, 1960.
3. Carton, C. A., Kessler, L. A., Seidenberg, B., and Hurwitt, E. S.: A plastic adhesive method of small blood vessel surgery. *World Neuro.* 1:356, 1960.
4. Ellis, R. A., and Levine, A. M.: Experimental sutureless ocular surgery. *Am. J. Ophthalmol.* 55:733, 1963.
5. Bloomfield, S., Barnert, A. H., and Kanter, P. D.: The use of Eastman 910 monomer as an adhesive in ocular surgery. I. Biologic effects on ocular tissues. *Am. J. Ophthalmol.* 55:742, 1963.
6. Hirst, L. W., and de Juan, E.: Sodium hyaluronate and tissue adhesive in treating corneal perforations. *Ophthalmology* 89:1250, 1982.
7. Refojo, M. F., Dohlman, C. H., Ahmad, B., Carroll, J. M., and Allen, J. C.: Evaluation of adhesives for corneal surgery. *Arch. Ophthalmol.* 80:645, 1968.
8. Webster, R. G., Slansky, H. H., Refojo, M. F., Boruchoff, S. A., and Dohlman, C. H.: The use of adhesive for closure of corneal perforations. *Arch. Ophthalmol.* 80:705, 1969.
9. Kenyon, K. R., Berman, M., Rose, J., and Gage, J.: Prevention of stromal ulceration in the alkali burned rabbit cornea by glued-on contact lens. Evidence for the role of polymorphonuclear leukocytes in collagen degradation. *Invest. Ophthalmol. Vis. Sci.* 18:570, 1979.
10. Gasset, A. R., Hood, I. C., Ellison, E. D., and Kaufman, H. E.: Ocular tolerance to cyanoacrylate monomer tissue adhesive analogues. *Invest. Ophthalmol. Vis. Sci.* 9:3, 1970.
11. Sani, B. P., and Refojo, M. F.: B14 C-isobutyl 2-cyanoacrylate adhesive. Determination of absorption in the cornea. *Arch. Ophthalmol.* 87:216, 1972.
12. Aronson, S. B., McMasters, P. R., Moore, T. E., Jr., and Coon, M. A.: Toxicity of the cyanoacrylates. *Arch. Ophthalmol.* 84:342, 1970.
13. Woodward, S. C., Hermann, J. B., Cameron, J. L., Brandes, G., Pulaski, E. J., and Leonard, F.: Histotoxicity of cyanoacrylate tissue adhesive in the rat. *Ann. Surg.* 162:113, 1965.
14. Refojo, M. F., Dohlman, C. H., and Koliopoulos, J.: Adhesives in ophthalmology. A review. *Surv. Ophthalmol.* 15:217, 1971.
15. Cameron, J. L., Woodward, S. C., Pulaski, E. J., Sleeman, H. K., Brandes, G., Kulkarni, R. K., and Leonard, F.: The degradation of cyanoacrylate tissue adhesive. I. *Surgery* 58:424, 1965.
16. Leonard, F., Kulkarni, R. K., Brandes, G., Nelson, J., and Cameron, J. J.: Synthesis and degradation of poly alkyl alpha-cyanoacrylates. *J. Appl. Polymer Sci.* 10:259, 1966.
17. Woodward, S. C.: Physiological and biochemical evaluation of implanted polymers. *Ann. N.Y. Acad. Sci.* 146:225, 1968.
18. Refojo, M. F.: Surgical adhesives in ophthalmology. *J. Macromol. Sci. Chem.* A4:667, 1970.
19. Refojo, M. F., Dohlman, C. H., Ahmad, B., Carroll, J. M., and Allen, J. C.: Evaluation of adhesives for corneal surgery. *Arch. Ophthalmol.* 80:645, 1968.
20. Fassett, D. H., Randabush, R. L., Emley, I. C., and Graulich, L. B.: Microbiological growth from Eastman 910 monomer and adhesives. *Cohesive News* 1:5, 1961.
21. Kaplan, G., and Borchardt, K. A.: The antibacterial properties of methyl 2-cyanoacrylate in the nonsuture closure of experimentally infected

wounds. Preliminary report. *Plast. Reconstr. Surg.* 38:507, 1966.

22. Jandinski, J., and Sonis, S.: In-vitro effects of isobutyl cyanoacrylate on four types of bacteria. *J. Dent. Res.* 50:1557, 1971.
23. Rietveld, E. C., Garnaat, M. A., and Seutter-Berlage, F.: Bacterial mutagenicity of some methyl 2-cyanoacrylates and methyl 2 cyano-3-phenylacrylates. *Mutat. Res.* 188:97, 1987.
24. Leyman, R. A. W., West, R. L., and Leonard, F.: Toxicity of alkyl 2-cyanoacrylates. II. Bacterial growth. *Arch. Surg.* 93:447, 1966.
25. Page, R. C., and Borick, P. M.: Contamination and recovery of bacterial spores from methyl 2-cyanoacrylate monomer. *Arch. Surg.* 94:162, 1967.
26. Matsumoto, T., Dobek, A. S., Pani, K. C., Kovarik, K. J., and Hamit, H. F.: Bacteriologic study of cyanoacrylate tissue adhesive. *Arch. Surg.* 97:527, 1968.
27. Eiferman, R. A., and Snyder, J. W.: Antibacterial effect of cyanoacrylate glue. *Arch. Ophthalmol.* 101:958, 1983.
28. Hogt, A. H., Dankert, J., de Vries, J. A., and Feijen, J.: Adhesion of coagulase negative staphylococci to biomaterials. *J. Gen. Microbiol.* 129:2959, 1983.
29. Olson, M. E., Ruseska, I., and Costerton, J. W.: Colonization of n-butyl-2-cyanoacrylate tissue adhesive by *Staphylococcus epidermidis*. *J. Biomed. Mater. Res.* 22:485, 1988.
30. Nassif, A. C.: An adhesive for repair of tissues. *J. Surg. Res.* 5:108, 1966.
31. Papatheofanis, F. J.: Cytotoxicity of alkyl-2-cyanoacrylate adhesives. *J. Biomed. Mater. Res.* 23:661, 1989.
32. Wahlig, H., Dingeldein, E., and Bergmann, R.: The release of gentamicin from polymethacrylate beads. *J. Bone Joint Surg.* 60:270, 1978.
33. Shenk, J. S., Ney, A. L., Tsukayama, D. T., Olson, M. E., and Bubrick, M. P.: Tobramycin-adhesive in preventing and treating PTFE vascular graft infections. *J. Surg. Res.* 47:487, 1989.

Role of Cell-Mediated Immunity to Staphylococci in Blepharitis

Linda Ficker, F.R.C.S., Meenakshi Ramakrishnan, M.Sc., David Seal, M.D.,
and Peter Wright, F.R.C.S.

We studied cell-mediated immunity to staphylococcal antigens in 116 patients with chronic blepharitis and eight normal subjects. Antibodies in tears and blood were measured. Enhanced cell-mediated immunity to *Staphylococcus aureus* was demonstrated in 46 of 116 patients (40%) in the absence of antibodies to teichoic acid but not among normal subjects. Symptoms of grittiness and morning stickiness were more frequent among patients without enhanced responses. Folliculitis occurred more commonly among patients with enhanced immunity. Marginal keratitis occurred equally among patients with and without enhanced systemic immunity, but patients with enhanced response more commonly required topical corticosteroid therapy. Desensitization to staphylococcal antigens could be investigated as a potential therapeutic approach in selected patients.

THE RELATIONSHIP between *Staphylococcus aureus* on the eyelids and the development of marginal keratitis, associated with blepharitis, has been reported by Thygeson,¹ Hogan and associates,² and Mondino.³ The marginal ulcers were culture-negative and ascribed to hypersensitivity to *S. aureus*. Corneal ring infiltrations can be created in a rabbit model. The rabbits must first be immunized with whole *S. aureus* cells, and antigen is then injected into the cornea. Mondino, Caster, and Dethlefs⁴ produced a rabbit model of ulcerative blepharitis that required previous immunization with *S. aureus* cell walls, which gave a proven cell-

mediated response, followed by prolonged topical application of viable *S. aureus*. This model could not be repeated with *S. epidermidis*, although a cell-mediated response was elicited in the rabbit.⁵ Mondino and Kowalski⁶ demonstrated corneal phlyctenulae and catarrhal infiltrates in rabbits systemically immunized with staphylococcal cell walls or ribitol teichoic acid-sensitized sheep red blood cells. The animals were then challenged with topical suspensions of viable *S. aureus* administered into the conjunctival fornix. The experiments failed unless the rabbits were first immunized to give a cell-mediated response.^{6,7}

Boe⁸ examined patients with chronic *S. aureus* infections and found they had exaggerated reactions, including sterile abscesses, to heat-killed, whole cell, staphylococcal vaccines. Martin, Crowder, and White⁹ investigated cell-mediated immunity to *S. aureus* protein A in the human. Mudd, Taubler, and Baker¹⁰ desensitized such a cell-mediated immune response by giving patients repeated injections of filtered staphylococcal phage lysate. White and Noble¹¹ compared the cutaneous reaction to purified staphylococcal protein A in normal subjects and patients with atopy or psoriasis and established the expected cell-mediated immune response for normal subjects. Dougherty and McCulley¹² devised a clinical classification of blepharitis of various causes. We treated 116 patients with chronic blepharitis of various causes, of whom 37 had marginal keratitis. We studied their humoral and cellular immune response to staphylococcal antigens.

Patients and Methods

After obtaining informed consent, we examined 116 patients with chronic blepharitis. Of these patients, 37 also had recurrent marginal keratitis. The patients were selected randomly

Accepted for publication Dec. 20, 1990.

From the Institute of Ophthalmology, Moorfields Eye Hospital, London, England. This study was supported in part by Fight for Sight.

Reprint requests to Peter Wright, F.R.C.S., Moorfields Eye Hospital, City Road, London EC1V 2PD, England.

from the External Diseases Clinic of our institution. There were no exclusion criteria, and patients were recruited with disease in both the acute and chronic phases. Before testing cell-mediated immunity, a clinical history was taken, and symptoms were scored on a scale 0 to 3 (absent, mild, moderate, or severe). Slit-lamp examination was performed, and clinical signs were graded for right and left, upper and lower eyelids, conjunctiva, and cornea from 0 to 3 (absent, mild, moderate, or severe), with a maximum score of 12. Tears (20 to 50 μ l) were collected on cellulose sponges and stored in plastic vials. Each sample was subsequently centrifuged to remove the sponge, and the tears were stored at -50°C . Blood (10 ml) was collected, and serum was stored at -50°C .

Cultures were collected from the eyelash roots of each patient by a semiquantitative soluble swab technique.¹³ Calcium alginate swabs were used, which dissolved in 3 ml of Ringer's saline when shaken vigorously. Additionally, eyelid cultures were collected by an eyelid scrub technique with broth-soaked swabs. Swabs, or 0.5 ml of solubilized swab in saline, were plated out onto horse blood agar. For solubilized swabs, numbers of colonies were expressed as colony forming units per milliliter of solubilized swab. *Staphylococcus aureus* was identified provisionally by an agglutination method, using latex particles coated with fibrinogen and IgG and confirmed by the tube coagulase test.

We tested 116 patients and eight normal adult subjects (without blepharitis or atopy and with normal vision) for cell-mediated immunity to staphylococcal antigens. Each patient received intradermal tests in the forearm with 0.1 ml of the staphylococcal suspensions and 0.05 ml of the protein A preparation. Suspensions of *S. aureus* (National Collection of Type Cultures 6571) and *S. epidermidis* (National Collection of Type Cultures 7292) were prepared from heat-killed cultures and diluted to 5×10^8 cells/ml in saline preserved with phenol. Protein A was freshly prepared and diluted in eyedrop saline and preserved with thimerosal (0.001%) to 50 ng/ml from a purified, freeze-dried preparation. Each patient also received control intradermal injections, one with 0.1 ml of phenol-preserved saline and one with 0.05 ml of thimerosal-preserved saline. Early results for wheal and flare were recorded at 15 minutes, and late swelling with central induration, which signified cell-mediated immunity, was recorded at 48 hours.

We investigated the humoral response by developing an enzyme-linked immunosorbent assay for measuring antibodies to *S. aureus* and *S. epidermidis* teichoic acid in serum and tears. Each staphylococcal antigen was prepared in our laboratory from cultures of *S. aureus* Wood 46 (coagulase-positive), which lacks the protein A antigen,^{14,15} and *S. epidermidis* biotype II (coagulase-negative), isolated from the eyelid of a patient with blepharitis. Cultures of each strain were incubated in nutrient broth at 37°C in 4% carbon dioxide for 48 hours with frequent shaking. Cells were centrifuged and washed twice with phosphate-buffered saline at pH 6.5. The cells were then sonicated for 12 hours at an amplitude of 121 μm in a constantly cooled vessel. Glass beads were placed with the cells in the inner chamber. The cells were respun in phosphate-buffered saline at pH 6.5, and the debris was discarded. Dilute hydrochloric acid was added to the extract and the precipitate, which formed at pH 4.2, was removed by centrifugation. The teichoic acid (polysaccharide) was precipitated from the supernatant with five times its volume of alcohol at pH 5.2¹⁶ and centrifuged. The alcohol was removed by evaporation, and the pellet was dissolved in phosphate-buffered saline at a concentration of 1 mg/ml to produce purified antigen.

In the enzyme-linked immunosorbent assay test, microtiter plates were coated with 100 μ l of each staphylococcal teichoic acid antigen at 20 $\mu\text{g}/\text{ml}$ in phosphate-citrate buffer at pH 9.6. The plate was sealed with tape and left overnight at 4°C . The plate was washed four times with phosphate-buffered saline/Tween (0.05%). Dilutions (100 μ l) of serum (1:10 to 1:12,800) or tears (1:40 to 1:640) in phosphate-buffered saline/Tween were added in duplicate, together with positive and negative controls, to each plate, which was sealed and incubated at 22°C for four hours. The plate was again washed four times with phosphate-buffered saline/Tween. Peroxidase-labeled rabbit antiserum (100 μ l) to human IgG/IgA kappa and lambda fraction, diluted 1:100 in phosphate-buffered saline/Tween, were added with a negative saline control to each well of the plate, which was incubated at 22°C for two hours. The plate was washed four times with distilled water. Orthophenylene diamine substrate was made at 8 mg/40 ml of phosphate-citrate buffer at pH 9.6, together with 100 μ l of 3% hydrogen peroxide. This solution (100 μ l) was added to each well, and optical density was

measured after 30 minutes at 450 nm. Statistical analyses were performed using Student's *t*-tests and chi-square tests as appropriate.

Results

The control group consisted of eight normal subjects, four men and four women, with a mean age of 33 years. The cell-mediated response of these subjects to protein A ranged from 0 to 6 mm.

Patients were divided into three groups according to their cell-mediated immunity, as determined by their skin reactions to protein A. Of 116 patients, 69 were classified as having a normal response. There were 35 men and 34 women, with a mean age of 51 years. The cell-mediated response of these patients to protein A ranged from 0 to 19 mm. Twenty-eight patients were classified as having an enhanced response. There were 18 men and ten women, with a mean age of 50 years. The cell-mediated response of these patients to protein A ranged from 20 to 60 mm. Nineteen patients were classified as having an extremely enhanced response. There were ten men and nine women, with a mean age of 39 years. The cell-mediated response of these patients to protein A was greater than 60 mm. There was no relationship between the groups with regard to mean ages or sex.

The cell-mediated responses of control subjects and patients to protein A, *S. aureus*, and *S. epidermidis* are shown in Table 1. The values for normal subjects were similar to those of the patients of White and Noble.¹¹ Of 116 patients, 28 (24%) and 19 (16%) had enhanced and extremely enhanced reactions compared to the 69 patients (60%) who had a normal response ($P = .001$). Patients with an enhanced reaction to protein A gave similar significant enhancement to whole *S. aureus* cells ($P = .001$) but not to *S. epidermidis*, whereas patients with a normal response to protein A and normal subjects had little response to either type of *Staphylococcus* species.

Treatment with antibiotics and corticosteroids at the time of examination was similar between the patient groups. None of the eight control subjects were taking any type of treatment. Of the 69 patients with a normal cell-mediated response, 16 were taking topical antibiotics, 17 were taking systemic antibiotics, 19 were taking topical corticosteroids, and two

TABLE 1
CELL-MEDIATED IMMUNE RESPONSES OF CONTROL SUBJECTS AND PATIENTS

GROUP (BASED ON RESPONSE TO PROTEIN A)	PROTEIN A (MM)		S. AUREUS (MM)		S. EPIDERMIDIS (MM)	
	MEAN	S.D.	MEAN	S.D.	MEAN	S.D.
Control subjects (N = 8)	3.9	6.3	3.1	1.9	0.25	0.66
Normal response (N = 69)	4.2	5.5	2.8	3.8	0.7	1.1
Enhanced response (N = 28)	42.9	11.2	5.4	4.7	0.9	1.6
Extremely enhanced response (N = 19)	88.4	16.5	6.5	4.8	1.6	1.8

were taking systemic corticosteroids. Of the 28 patients with an enhanced cell-mediated response, six were taking topical antibiotics, eight were taking systemic antibiotics, seven were taking topical corticosteroids, and two were taking systemic corticosteroids. Of the 19 patients with an extremely enhanced cell-mediated response, two were taking systemic antibiotics, and six were taking topical corticosteroids.

Isolation of *S. aureus* from eyelids has previously been reported in normal subjects.^{13,17} Badiani and associates¹³ isolated *S. aureus* by the soluble swab technique in six of 100 subjects. Seal, Barrett, and McGill¹⁷ isolated *S. aureus* by the scrub technique in two of 30 subjects. Isolation was more frequent by the eyelid scrub technique, which was used for comparison in 80 of the patients, than by the soluble swab collection method, which was used in all 116 patients. *Staphylococcus aureus* was isolated by the scrub technique in 11 of 49 patients with a normal response, five of 19 patients with an enhanced response, and three of 12 patients with an extremely enhanced response. *Staphylococcus aureus* was isolated by the soluble swab technique in six of 69 patients with a normal response, three of 28 patients with an enhanced response, and two of 19 patients with an extremely enhanced response. No qualitative or quantitative difference in isolation rates was demonstrated between patients with varying cell-mediated immunity to protein A. *Staphylococcus epidermidis* was isolated from

the eyelid margins of all patients, and this compared with a previous study of 100 normal subjects.¹³

Patients were also divided in two groups with respect to their cell-mediated response to killed *S. aureus* cells at less than 5 mm and greater than 6 mm. Of the eight control subjects, their cell-mediated response to killed *S. aureus* at 48 hours ranged from 2.0 to 7.0 mm, with a mean value of 3.1 ± 1.9 mm. Of the 116 patients, 82 were classified as having a normal cell-mediated response to killed *S. aureus*. Their response was less than 5 mm, with a mean value of 2.0 ± 2.1 mm. Of these 82 patients, 26 (31%) had an enhanced or extremely enhanced response to protein A. The remaining 34 patients were classified as having an enhanced cell-mediated response to killed *S. aureus*. Their response was greater than 6 mm, with a mean value of 9.5 ± 4.1 mm. Of these 34 patients, 21 (72%) had an enhanced or extremely enhanced response to protein A. The difference between patient groups showing normal and enhanced responses to killed *S. aureus* was significant ($P = .001$). The comparison of the protein A reactions in these groups was also significant ($P = .01$).

The occurrence of serum and tear antibodies to teichoic acids of *S. aureus* and *S. epidermidis* was determined by the enzyme-linked immunosorbent assay test, with patients grouped according to their cell-mediated response to protein A (Table 2). No significant difference

TABLE 2
MEDIAN SERUM TITERS AND DETECTION OF
ANTIBODIES IN TEARS OF CONTROL SUBJECTS AND
PATIENTS

GROUP (BASED ON RESPONSE TO PROTEIN A)	MEDIAN SERUM TITER FOR <i>S.</i> <i>AUREUS</i> TEICHOIC ACID	MEDIAN SERUM TITER FOR <i>S.</i> <i>EPIDERMIDIS</i> TEICHOIC ACID	DETECTION OF ANTIBODIES TO <i>S.</i> <i>AUREUS</i> TEICHOIC ACID IN TEARS
Control subjects (N = 8)	1:200	1:120	2
Normal response (N = 69)	1:100	1:75	15
Enhanced response (N = 28)	1:75	1:75	5
Extremely enhanced response (N = 19)	1:75	1:75	2

TABLE 3
MEAN SCORES OF SYMPTOMS ACCORDING TO THE
CELL-MEDIATED RESPONSES TO PROTEIN A

SYMPTOMS (MAXIMUM = 3)	CELL-MEDIATED RESPONSE TO PROTEIN A			P VALUE* (CHI- SQUARE TEST)
	NORMAL (N = 69)	ENHANCED (N = 28)	EXTREMELY ENHANCED (N = 19)	
Grittiness	0.84	0.64	0.2	.001
Stickiness	0.77	0.64	0.3	.02
Burning	0.58	0.64	0.3	NS
Sore	0.84	1.03	1.0	NS
Blurred vision	0.38	0.18	0.32	NS
Red (inflamed)	0.52	0.43	0.37	NS

*Significance between patients with normal and extremely enhanced response to protein A. NS indicates not significant.

was noted between control subjects and patient groups.

The symptoms of the patients were scored and mean values are given in Table 3. Sensations of grittiness and early morning stickiness were more frequently found in patients with a normal response to protein A compared with patients with an extremely enhanced response ($P = .001$ and $P = .02$, respectively). No significant differences were found for patients with moderate enhancement compared with either the normal or extremely enhanced group.

The clinical signs were similarly scored and mean values are given in Table 4. Folliculitis, eyelash follicle inflammation with purulent discharge, was more commonly found in patients with an extremely enhanced response to protein A ($P = .001$). Other signs of chronic inflammation were similar between the groups. No significant differences were found for patients with moderate enhancement compared with either the normal or extremely enhanced group. Acne rosacea was noted in five of 69 (7%), one of 28 (4%), and two of 19 (10%) patients with normal, enhanced, and extremely enhanced cell-mediated immunity to protein A, respectively.

Patients with marginal corneal epithelial disease, including previous marginal ulceration and scarring, are considered in Table 5. The occurrence was not statistically different between patients with and without enhanced cell-mediated immunity to protein A. Requirement for treatment with topical corticosteroids, however, may be greater in the enhanced group than in the group with a normal response to

TABLE 4
MEAN SCORES OF SIGNS ACCORDING TO THE
CELL-MEDIATED RESPONSES TO PROTEIN A

SIGNS (MAXIMUM = 12)	CELL-MEDIATED RESPONSE TO PROTEIN A			P VALUE* (CHI- SQUARE TEST)
	NORMAL (N = 69)	ENHANCED (N = 28)	EXTREMELY ENHANCED (N = 19)	
Folliculitis	0.19	0.2	1.2	.001
Collarettes	5.9	6.3	6.2	NS
Eyelash misdirection	2.7	2.8	2.4	NS
Eyelash loss	1.4	1.4	1.5	NS
Seborrhea	2.5	2.1	2.8	NS
Telangiectasia	6.6	3.4	7.1	NS
Meibomian plugging	6.0	3.4	5.5	NS
Meibomianitis	0.09	0.03	—	NS
Marginal eyelid inflammation	3.9	4.2	4.5	NS
Marginal eyelid thickening	4.5	4.5	4.7	NS
Conjunctival migration	5.0	5.4	4.4	NS
Marginal corneal vascularization	1.8	1.8	1.3	NS

*Significance between patients with normal and extremely enhanced response to protein A. NS indicates not significant.

protein A (11 of 15 and ten of 22, respectively; chi-square test, 2.8; $P = .05$). These results are biased, however, since nine of 47 patients (19%) with a normal response to protein A were on corticosteroid treatment in the absence of marginal epitheliopathy compared to two of 32 (6%) in the enhanced group (chi-square test, 2.7; $P = .1$).

Discussion

Of our 116 patients with chronic blepharitis of mixed origin, 47 (40%) had enhanced cell-mediated immunity to *S. aureus* protein A antigen. These results differ from those found in normal subjects in our study as well as those of White and Noble.¹¹ This cell-mediated response can be tested with either protein A antigen or killed whole *S. aureus* cells. Although there is good correlation between the response to the two antigens, each is best tested separately. A cell-mediated response to *S. epidermidis* did not

occur, possibly because it lacks protein A in its cell wall. Protein A gave a wheal reaction at 15 minutes in all patients and normal subjects tested, probably because of crossbinding of fragment crystallizable receptors of IgE on mast cells.

We analyzed the symptoms and signs of the patients in relation to their cell-mediated immune status to *S. aureus* protein A antigen (Tables 3 and 4). Our patients represented a mixed group, with chronic eyelid inflammation ascribed clinically to staphylococcal disease and sometimes associated with seborrhea. Early morning stickiness, described by McCulley, Dougherty, and Deneau¹⁸ as typical of meibomianitis, was more frequent in patients with a normal cell-mediated immune status as was the sensation of grittiness. The only sign that correlated with extremely enhanced cell-mediated immunity was eyelash folliculitis, which has been described previously for hair follicles at other sites.⁸ Unfortunately, it has not been possible to identify other clinical subgroups of patients with chronic blepharitis that correlate with cell-mediated immunity. It has been shown that cell-mediated immunity to *S. epidermidis* does not occur in either normal subjects or those with chronic blepharitis. Clinical classification of chronic blepharitis can thus be expected to be descriptive rather than as a function of their immune status with respect to staphylococcal antigen. Our aim was to test whether possession of cell-mediated immunity

TABLE 5
PATIENTS WITH MARGINAL CORNEAL EPITHELIAL
DISEASE

GROUP (BASED ON RESPONSE TO PROTEIN A)	MARGINAL KERATOPATHY*		NO MARGINAL KERATOPATHY	
	USING CORTICO- STEROID	NOT USING CORTICO- STEROID	USING CORTICO- STEROID	NOT USING CORTICO- STEROID
Normal response (N = 69)	10	12	9	38
Enhanced response (N = 28)	5	2	2	19
Extremely enhanced response (N = 19)	6	2	0	11

*Includes previous marginal ulceration and scarring.

to *S. aureus* or *S. epidermidis* could provide an alternative basis to classify patients.

No relationship between enhanced cell-mediated immunity to *S. aureus* and marginal ulceration was found, but the enhanced group were found more likely to require treatment with corticosteroids. Marginal keratitis has been ascribed to cell-mediated immunity, since there are sterile infiltrates that may represent an immune response to staphylococci on the eyelids. Patients with marginal ulceration were not followed up on a longitudinal basis, and some had been receiving corticosteroid treatment for months or years when examined. Some patients with a documented history of marginal keratitis did not demonstrate systemic cell-mediated immunity to staphylococcal antigen. Local and systemic responses may represent different stages of the natural course. It is not clear whether patients with enhanced cell-mediated immunity to *S. aureus* and recurrent marginal ulceration, which requires treatment with corticosteroids, would benefit from desensitization.^{10,19} Our results suggest that this alternative approach to therapy is worthy of trial as a specialist procedure.

No relationship between the cell-mediated immune status to *S. aureus* antigen and titer of serum (predominantly IgG) or tear (predominantly IgA) antibody to ribitol-teichoic acid was found. This is not surprising and occurs in other types of cell-mediated immunity, such as tuberculosis. Mondino, Caster, and Dethlefs⁴ found high serum titers to ribitol-teichoic acid in frequently immunized rabbits. This represents an acute exposure, differing from the human who has been exposed to the antigen intermittently over many years. Additionally, no relationship was found between the isolation of *S. aureus* from eyelids and the cell-mediated immune status of the patient. Kappler, Kotzin, and Herron,²⁰ however, have identified T-cell stimulation by *S. aureus* toxins, which act on specific sequences of their receptors for major histocompatibility complex protein-associated antigen. The authors suggest that this may influence the reaction of different individuals to the presence of such staphylococcal toxins, which will thus interrelate with the cell-mediated immunity of the patient.

If it is considered an absolute requirement that systemically expressed cell-mediated immunity be present to *S. aureus* antigen as in the rabbit model,⁴ then our results suggest that this is not true. Of 116 randomly selected patients with chronic blepharitis, 69 (60%) did not have

systemic cell-mediated immunity to *S. aureus* antigen. For the remaining 47 patients (40%), systemic cell-mediated immunity to *S. aureus* antigens may have been a contributory factor. Local cell-mediated immune responses to *S. aureus* antigen could be investigated by relevant cell biology techniques.

The use of topical corticosteroids for patients with marginal keratitis appears correlated with cell-mediated immunity to *S. aureus*, particularly to protein A. Systemic cell-mediated immunity may result from repeated episodes of *S. aureus* infection or colonization. Cell-mediated immunity, expressed as delayed-type hypersensitivity, has been found to be involved with the pathogenesis of blepharitis that features folliculitis. To this extent there is a similarity to the rabbit model.⁴

References

1. Thygeson, P.: Marginal corneal infiltrates. *Trans. Am. Acad. Ophthalmol.* 51:198, 1946.
2. Hogan, M. J., Diaz-Bonnet, V., Okumoto, M., and Kimura, S. J.: Experimental staphylococcal keratitis. *Invest. Ophthalmol.* 1:267, 1962.
3. Mondino, B. J.: Inflammatory diseases of the peripheral cornea. *Ophthalmology* 95:463, 1988.
4. Mondino, B. J., Caster, A. I., and Dethlefs, B.: A rabbit model of staphylococcal blepharitis. *Arch. Ophthalmol.* 105:409, 1987.
5. Mondino, B. J., and Adamu, S.: Ocular immune response to *Staphylococcus epidermidis*. In Cavanagh, D. H. (ed.): *The Cornea. Transactions of the World Congress on the Cornea III*. New York, Raven Press, 1988, pp. 431-433.
6. Mondino, B. J., and Kowalski, R. P.: Phlyctenulae and catarrhal infiltrates. Occurrence in rabbits immunized with staphylococcal cell walls. *Arch. Ophthalmol.* 100:1968, 1982.
7. Mondino, B. J., and Dethlefs, B.: Occurrence of phlyctenules after immunization with ribitol teichoic acid of *Staphylococcus aureus*. *Arch. Ophthalmol.* 102:461, 1984.
8. Boe, J.: Investigations on the importance of bacterial allergy for the development of cutaneous infections due to staphylococci. *Acta Derm. Venereol.* 26:111, 1945.
9. Martin, R. R., Crowder, J. G., and White, A.: Human reactions to staphylococcal antigens. *J. Immunol.* 99:269, 1967.
10. Mudd, S., Taubler, J. H., and Baker, A. G.: Delayed-type hypersensitivity to *Staphylococcus aureus* in human subjects. *J. Reticul. Endothel. Soc.* 8:493, 1970.
11. White, M. I., and Noble, W. C.: The cutaneous reaction to staphylococcal protein A in normal sub-

jects and patients with atopic dermatitis or psoriasis. *Br. J. Dermatol.* 113:179, 1985.

12. Dougherty, J. M., and McCulley, J. P.: Comparative bacteriology of chronic blepharitis. *Br. J. Ophthalmol.* 68:524, 1984.

13. Badiani, D., Bron, A., Elkington, A., Lea, S. H., Playfare, C., Preziosi, J., Seal, D. V., Walters, R., and Wright, P.: Use of a novel transport method for the quantification of the normal flora of the external eye. *Microbiol. Ecol. Health Dis.* 1:57, 1988.

14. Burnet, F. M.: The exotoxins of *Staphylococcus pyogenes aureus*. *J. Pathol.* 32:717, 1929.

15. Haukenes, G.: Serological typing of *Staphylococcus aureus*. *Acta Pathol. Microbiol. Scand.* 61:415, 1964.

16. Haukenes, G., Losnegard, N., and Oeding, P.: Extraction and fractionation of antigenic material from *Staphylococcus aureus*. *Acta Pathol. Scand.* 53:84, 1961.

17. Seal, D. V., Barrett, S. P., and McGill, J.: Etiology and treatment of acute bacterial infection of the external eye. *Br. J. Ophthalmol.* 66:357, 1982.

18. McCulley, J. P., Dougherty, J. M., and Deneau, D. G.: Classification of chronic blepharitis. *Ophthalmology* 89:1173, 1982.

19. Eiser, N.: Desensitization today. *Br. Med. J.* 300:1412, 1990.

20. Kappler, J., Kotzin, B., and Herron, L.: V-beta specific stimulation of human T cells by staphylococcal toxins. *Science* 244:811, 1989.

OPHTHALMIC MINIATURE

... I sat by the board and made all the moves: he would call his move, I would place the piece as he directed, and then I would tell him my counter-move. When he had beaten me he would go back over the game and tell me precisely the point at which I had gone wrong. I was awed by such a memory and such a spatial sense in a man who lived in darkness; he was contemptuous of me when I could not remember what I had done six or eight moves back, and of sheer necessity I had to develop the memory-trick myself.

Robertson Davies, *The Deptford Trilogy. The Manticore.*
New York, Penguin, 1983, p. 465

Herpes Simplex Dendritic Keratitis After Keratoplasty

Mark J. Mannis, M.D., Ronald D. Plotnik, M.D., Ivan R. Schwab, M.D.,
and R. Dale Newton, B.A.

We treated three patients with herpes simplex dendritic keratitis that occurred between three and 11 months after keratoplasty. The patients had no history of herpetic infection. The eyes of two of the patients were grafted for corneal scarring of undetermined origin. The eye of the third patient was grafted for pseudophakic bullous keratopathy. At the time of onset of dendritic keratitis, all three patients were receiving either maintenance or higher doses of topical corticosteroids. All infections responded to topical antiviral treatment. The findings in these patients illustrate the importance of considering herpes simplex keratitis in the differential diagnosis of all late-onset epithelial defects in the corneal graft, even in the absence of a history of herpes simplex keratitis.

THE RECURRENCE of active dendritic keratitis in patients after penetrating keratoplasty performed for the sequelae of herpes simplex virus infection is a well-documented postoperative complication of the procedure. The rate of recurrence of active herpes simplex infection after corneal transplantation in such patients has been variably reported between 6% and 75%.¹⁻⁸ The corneal surgeon is generally vigilant for the recurrence of active herpetic disease in the eye that has been grafted for herpes simplex and is being treated with topical corticosteroids. Accordingly, prophylaxis with antiviral agents is used routinely for varying periods of time postoperatively.⁸ Although the occurrence of ocular herpes simplex infections has been described in

eyes grafted without previous history of manifest herpes simplex infection,⁹ recurrences of the virus are not expected in patients in whom herpes simplex has not been a clinical problem. In such patients, postoperative epithelial defects caused by herpes simplex virus are not generally suspected.

Epithelial defects after corneal transplantation are, nonetheless, commonplace occurrences and are generally managed with ocular lubricants, patching, or bandage lenses that promote epithelial healing.⁸ We treated three cases of herpes simplex virus dendritic keratitis in corneal allografts of patients with no previous history of herpes simplex infection before corneal transplantation.

Case Reports

Case 1

A 71-year-old man was referred to our institution in January 1990 for a painful pseudophakic bullous keratopathy. The patient had undergone bilateral intracapsular cataract extraction 20 years earlier and had secondary anterior chamber intraocular lens implantation in both eyes seven years before his referral for corneal edema. The patient had a previous retinal detachment repaired in the left eye, a pars plana vitrectomy for vitreous strands to the incision, and macular grid photocoagulation for chronic cystoid macular edema. At the time of the initial examination, visual acuity was R.E.: 20/25 and L.E.: counting fingers. In the left eye, pertinent findings at the time of examination included central microcystic and bullous edema as well as moderate stromal edema. There was no evidence of corneal scarring, and there were several keratic precipitates. Corneal sensation was normal in both eyes as measured with a Cochet-Bonnet esthesiometer. There were signs of early peripheral corneal edema in the right eye as well.

On March 14, 1990, the patient underwent a combined penetrating keratoplasty and intra-

Accepted for publication Nov. 27, 1990.

From the Cornea and External Disease Service, Department of Ophthalmology, University of California, Davis, Sacramento, California. This study was supported in part by an unrestricted grant from Research to Prevent Blindness, Inc.

Reprint requests to Mark J. Mannis, M.D., Department of Ophthalmology, 1603 Alhambra Blvd., Sacramento, CA 95816.

ocular lens exchange in the left eye. The pathologic specimen from the recipient cornea showed changes consistent with pseudophakic bullous keratopathy. The corneal epithelium healed promptly after the operation and remained intact. The early postoperative course was uneventful. The patient returned two months later with foreign body sensation. The only medication taken was topical prednisolone sodium phosphate four times daily. The graft was clear; however, there were three small epithelial defects superiorly at the graft-host interface and a similar defect inferiorly. Immunofluorescent staining performed on corneal scrapings was positive for herpes simplex type I, and the patient was treated with trifluridine every two hours. Seven days later, he was reexamined, and the epithelium was noted to be intact. The antiviral medication was tapered over the next week and discontinued.

The patient continued to do well until July 12, 1990, when he again had foreign body sensation, a red eye, and subjectively decreased vision. He had a large geographic ulcer extending from the 8 o'clock to the 2 o'clock meridian along the graft-host interface and involving both donor and recipient cornea. Immunofluorescent antibody staining was once again positive for herpes simplex type I, and the patient was treated with topical trifluridine every two hours with complete resolution of the epithelial defect over the next ten days. At five months after keratoplasty, the graft remained clear.

Case 2

A 56-year-old man was referred to our institution in January 1989 for corneal transplantation after a previously failed graft performed for scarring secondary to a corneal ulcer of undetermined origin. Both the initial disease process and the previous keratoplasty were performed 20 years before the patient's referral. At the initial examination, visual acuity was R.E.: 20/100 and L.E.: 20/20. Pertinent findings included a normal external ocular examination with no evidence of abnormal skin or eyelid findings. Examination of the right eye disclosed a large graft with diffuse, patchy scarring throughout the stroma, stromal thinning, and the presence of both active and ghost vessels in the stroma. Corneal sensation was normal in both eyes as measured with a Cochet-Bonnet esthesiometer. Nuclear sclerosis and cortical lens opacities were noted in the right eye. Examination of the left eye was normal.

On March 21, 1989, the patient underwent a

combined penetrating keratoplasty, extracapsular cataract extraction, and posterior chamber intraocular lens implantation. Histopathologic examination of the recipient button was consistent with corneal scarring, stromal vascularization, and early band keratopathy.

The postoperative course was uneventful, and the graft remained clear. At 11 months postoperatively, best-corrected visual acuity had improved to 20/40. A regimen of topical corticosteroids was continued over this period and was tapered gradually to once daily. On May 8, 1990 (14 months postoperatively), the patient described a history of redness, tearing, and decreased vision for one week. Visual acuity had decreased to 20/400. There was diffuse mild conjunctival injection without discharge, moderate epithelial and stromal edema, moderate granulomatous (mutton fat) keratic precipitates, and a distinct inferior endothelial rejection line. Acute graft rejection was diagnosed, and the patient was treated with a subconjunctival injection of dexamethasone (2 mg), oral prednisone (60 mg daily for three days with tapering over one week), topical prednisolone sodium phosphate (1% every hour while awake), and dexamethasone ointment at bedtime. The patient was examined 48 hours later with slight improvement in visual acuity to 20/200. There was persistent moderate epithelial and stromal edema. Additionally, there were several small dendriform epithelial defects (Fig. 1). Corneal scrapings were taken for immunofluorescent antibody staining and viral culture, both of which were positive for herpes simplex type I.

Treatment with trifluridine every two hours was initiated, and topical corticosteroid therapy was decreased to every two hours. Four days later the epithelial defect was almost completely resolved, but corneal edema persisted. Trifluridine application was diminished to four times daily, and topical corticosteroid therapy was continued every two hours. There was no further recurrence of dendritic lesions of the cornea. The corneal edema, presumably resulting from the graft reaction, however, persisted despite continued topical corticosteroid therapy and antiviral prophylaxis with vidarabine ointment once daily. Visual acuity remained at 20/400.

Case 3

A 56-year-old man was referred to our institution for penetrating keratoplasty. The patient had a history of a corneal ulcer in the right eye

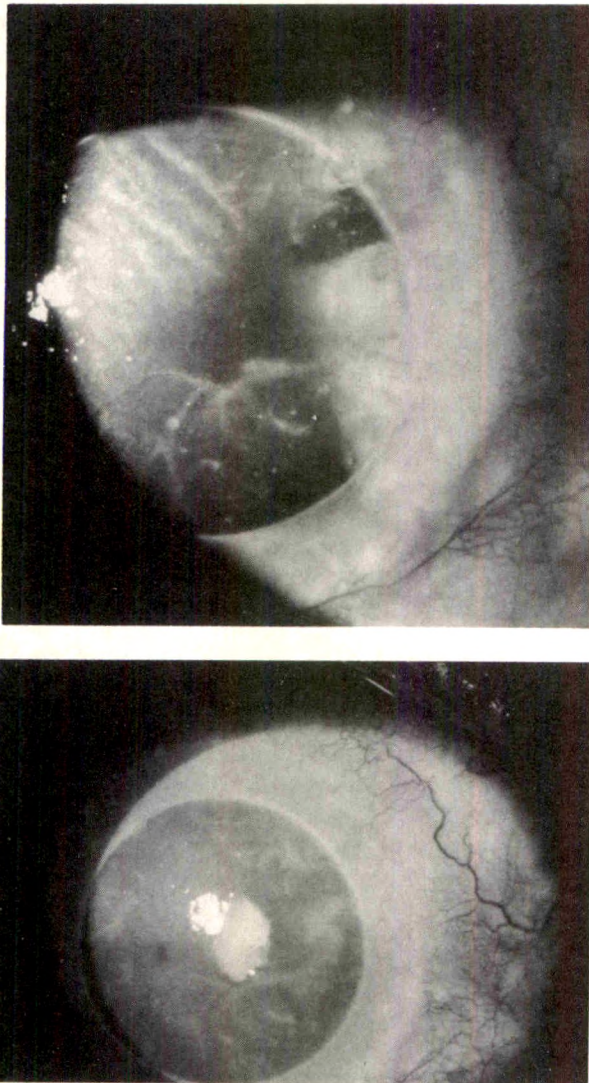


Fig. 1 (Mannis and associates). Case 2. Central corneal edema and keratic precipitates associated with graft reaction (top) accompanied by paracentral dendrites in graft (bottom).

of undetermined origin 31 years before his referral and a similar ulcer eight years before his referral. At the initial examination, visual acuity was R.E.: counting fingers and L.E.: 20/30-2. In the right cornea there was a full-thickness, axial, dense, gray-white corneal scar with slight stromal thinning. Corneal sensation was 5/6 using a Cochet-Bonnet esthesiometer. Background and preproliferative retinopathy was found on retinal examination.

On Dec. 20, 1989, the patient underwent an uncomplicated penetrating keratoplasty in the

right eye. Histopathologic examination of the excised cornea disclosed absence of Bowman's layer centrally with scarring and thinning of the stroma. The stroma was diffusely hypercellular with multiple stromal vessels. The initial postoperative course was uneventful, and visual acuity improved to 20/200 during the first four months postoperatively. On May 24, 1990 (five months postoperatively), the patient had a routine follow-up examination and had no ocular symptoms. Examination, however, disclosed a dendritic epithelial defect straddling the graft-host interface superotemporally (Fig. 2). Immunofluorescent antibody staining was positive for herpes simplex type I. The diagnosis established by immunofluorescent staining was confirmed by viral culture. The patient was treated with trifluridine every two hours, and topical prednisolone sodium phosphate was reduced from four times daily to three times daily. During the next two weeks, the epithelial lesion resolved completely, and the corneal graft remained clear.

Discussion

The occurrence of epithelial defects in the postoperative corneal graft may signal a variety of events. In the immediate postoperative period (one to ten days), epithelial defects are common and usually result from sloughing of donor epithelium or from intraoperative surgical trauma to the epithelium.^{8,10-12} Generally, these defects are of short duration and require minimal treatment.^{11,12} Conversely, epithelial defects occurring soon after surgery in patients with ocular surface abnormalities from conditions such as previous alkali burn or dry eye require assiduous care to promote epithelial healing and maintenance of epithelial integrity. Persistent epithelial defects represent a common cause of graft failure in patients with ocular surface disorders, including pemphigoid, Stevens-Johnson syndrome, aqueous-deficiency dry eye, alkali burns, infectious disorders such as herpes simplex and herpes zoster, chronic neurotrophic ulcers, poor incision apposition with graft override, and eyelid abnormalities.⁸ Late developing corneal epithelial defects, occurring more than one month postoperatively, are rare in grafted eyes with otherwise normal ocular surface and adnexa. Such defects usually result from trauma to the

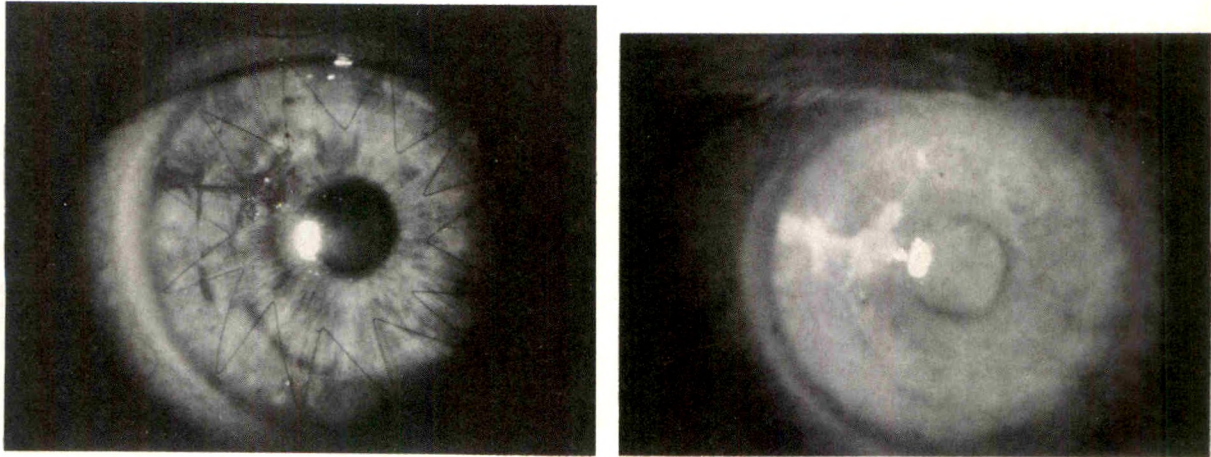


Fig. 2 (Mannis and associates). Case 3. Paracentral corneal dendrite in graft stained with rose bengal (left) and fluorescein (right).

epithelium from a hand or contact lens, medication toxicity, or, less commonly, an acute epithelial rejection reaction.¹³

The frequency of epithelial defects from recurrent epithelial herpes keratitis in the corneal graft has been reported in clinical reports to range from 6% to 75%¹⁻⁸ and may increase during periods of treatment with higher doses of corticosteroids.^{6,14} In patients with no previous history of herpes simplex keratitis, however, the occurrence of dendritic disease in the graft would not normally be expected. Salisbury and associates⁹ reported three cases of epithelial herpes infection after penetrating keratoplasty in patients with corneal opacities unrelated to herpes simplex virus infection. Each of their patients had undergone or was undergoing immune graft rejection. The authors concluded that herpes simplex infection should be considered in patients with an immunologically compromised graft, even in the absence of known herpetic disease, since allograft rejection may result in the activation of latent virus in the trigeminal ganglion. Only one of our patients, however, had an immune graft reaction associated with the development of herpes simplex virus keratitis.

We treated three patients with no history of herpes simplex keratitis. One patient had pseudophakic bullous keratopathy and no clinical suggestion of previous viral disease. Two patients (Cases 2 and 3) each had a history of corneal ulceration many years before keratoplasty but no documentation of cause. In the patient in Case 2, corneal sensation was normal, and the scarring was not the typical ante-

rior stromal scarring seen in herpes simplex. In the patient in Case 3, there was a history of a single recurrence of the corneal ulcer but no suggestion that this was herpetic in origin. In each of our patients, the diagnosis of herpes simplex keratitis was established only after unexpected occurrence of dendritic ulceration in the graft 1½ to five months postoperatively. In all three patients, the eye was being treated with topical prednisolone sodium phosphate 1%. Two patients (Cases 1 and 3) were receiving the medication four times daily. The other patient (Case 2) was being treated intensively with hourly doses of topical prednisolone sodium phosphate, a nightly dose of dexamethasone ointment, and 60 mg of systemic prednisone for the treatment of an acute graft reaction.

Since all three patients had new-onset dendritic keratitis within a 17-day period in May 1990, office records were checked carefully to determine whether the three patients were examined on the same day postoperatively near the time of onset of the herpes simplex infections to rule out a common source of infection. None of the patients was examined on the same day before or during this period. In a similar fashion, office attendance records were checked to determine whether the three patients visited the office in common with any patient with known herpetic keratitis. This analysis was also noncontributory. There was no evidence of herpetic whitlow in office personnel.

The findings in these patients demonstrate the importance of considering herpes simplex keratitis in the differential diagnosis of late-

onset epithelial defects after keratoplasty even in the absence of a history of herpes keratitis. Epithelial lesions or anterior uveitis caused by herpes simplex infection may be difficult to distinguish from epithelial defects from other causes in the graft eye or from the uveitis associated with immune graft reaction. We speculate that two of our patients (Cases 2 and 3) may indeed have had herpes simplex previously, although neither the history nor the physical findings suggested this diagnosis initially. In the third patient (Case 1), there was no suggestion of herpes simplex before its appearance more than one month after keratoplasty.

An important factor predisposing to the development of herpetic keratitis in these patients may have been the use of topical corticosteroids, which are routinely used in graft eyes as an antiinflammatory and immunosuppressive agent. Corticosteroids lower the threshold for herpetic infection,¹⁵ and in patients with latent herpes simplex, this may have permitted the emergence of active infection. This is of particular concern in the patient who was being treated with increased doses of topical corticosteroids (Case 2), who developed a graft reaction and required higher doses of corticosteroids. Alternatively, the development of epithelial defects in patients taking intensive corticosteroid regimens may result from the adverse effect of corticosteroids on epithelial healing.¹⁶ Collectively, the findings in these patients demonstrate the need to consider herpetic keratitis in the differential diagnosis of early- and late-onset postkeratoplasty epithelial defects with or without a history of previous herpes infection.

References

1. Pfister, R., Richards, J. S. F., and Dohlman, C. H.: Recurrence of herpetic keratitis in corneal grafts. *Am. J. Ophthalmol.* 73:192, 1972.
2. Polack, F. M., and Kaufman, H. E.: Penetrating keratoplasty in herpetic keratitis. *Am. J. Ophthalmol.* 73:908, 1972.
3. Langston, R. H. S., Pavan-Langston, D., and Dohlman, C.: Penetrating keratoplasty for herpetic keratitis. Prognostic and therapeutic determinants. *Trans. Am. Acad. Ophthalmol. Otolaryngol.* 79:77, 1975.
4. Foster, C. S., and Duncan, J.: Penetrating keratoplasty for herpes simplex keratitis. *Am. J. Ophthalmol.* 92:336, 1981.
5. Cohen, E. J., Laibson, P. R., and Arentsen, J. J.: Corneal transplantation for herpes simplex keratitis. *Am. J. Ophthalmol.* 95:645, 1983.
6. Cobo, L. M., Coster, D. J., Rice, N. S. C., and Jones, B. R.: Prognosis and management of corneal transplantation for herpetic keratitis. *Arch. Ophthalmol.* 98:1755, 1980.
7. Epstein, R. J., Seedor, J. A., Dreizen, N. G., Stulting, R. D., Waring, G. O., Wilson, L. A., and Cavanagh, H. D.: Penetrating keratoplasty for herpes simplex keratitis and keratoconus. *Ophthalmology* 94:935, 1987.
8. Wilson, S. E., and Kaufman, H. E.: Graft failure after penetrating keratoplasty. *Surv. Ophthalmol.* 34:325, 1990.
9. Salisbury, J. D., Berkowitz, R. A., Gebhardt, B. M., and Kaufman, H. E.: Herpesvirus infection of cornea allografts. *Ophthalmic Surg.* 15:406, 1984.
10. Gutow, A., Soong, H. K., Meyer, R. F., Sugar, A., and Musch, D. C.: Corneal epithelial healing after keratoplasty for herpes simplex keratitis. *Cornea* 5:5, 1986.
11. Meyer, R. F., and Bobb, K. C.: Corneal epithelium in penetrating keratoplasty. *Am. J. Ophthalmol.* 90:142, 1980.
12. Reed, D. B., Mannis, M. J., Hills, J., and Johnson, C. A.: Corneal epithelial healing after penetrating keratoplasty using topical Healon versus balanced salt solution. *Ophthalmic Surg.* 18:525, 1987.
13. Alldredge, O. C., and Krachmer, J. H.: Clinical manifestations of graft rejection. *Arch. Ophthalmol.* 99:599, 1981.
14. Ficker, L. A., Kirkness, C. M., Rice, N. S. C., and Steele, A. D. McG.: The changing management and improved prognosis for corneal grafting in herpes simplex keratitis. *Ophthalmology* 96:1587, 1989.
15. Baringer, J.: The biology of herpes simplex virus infection in humans. *Ophthalmology* 21:171, 1976.
16. Klein, R.: Pathogenic mechanisms of recurrent herpes simplex virus infections. *Arch. Virol.* 51:1, 1976.

Initial Glaucomatous Optic Disk and Retinal Nerve Fiber Layer Abnormalities and Their Progression

Anja Tuulonen, M.D., and P. Juhani Airaksinen, M.D.

We attempted to identify the initial glaucomatous changes of the optic disk and retinal nerve fiber layer and to analyze how these changes subsequently progressed. Of 61 eyes of 61 patients with ocular hypertension, 23 (38%) developed glaucoma during ten years of follow-up (range, five to 15 years). The initial sign of glaucomatous damage was diffuse enlargement of the optic disk cup in ten of 23 eyes or generalized thinning of the nerve fiber layer without localized changes in 12 of 23 eyes. We found localized optic disk damage in ten of 23 patients and localized retinal nerve fiber layer damage in 11 of 23 patients alone or in combination with diffuse damage. In 13 of 23 eyes, the cupping ended up in diffuse enlargement with even more profound thinning of the neural rim in the upper and lower temporal disk margins. There seems to be great variability in the appearance and progression of the initial glaucomatous optic disk and nerve fiber layer abnormalities in patients with increased intraocular pressure.

THE APPEARANCE of the glaucomatous optic nerve head depends on the number of ganglion cell axons. The loss of axons in glaucomatous eyes results in localized notching of the neural tissue, concentric enlargement of the optic cup, or both.¹⁻³ The glaucomatous damage is visible both in the retinal nerve fiber layer and the optic disk. Although the glaucomatous optic disk changes are well documented in numerous

cross-sectional studies,^{1,4} there are only a few longitudinal studies where the first detectable signs of axon damage and their progression in the optic disk have been defined.⁵⁻⁸ Even fewer studies have specifically investigated serial photographic changes in the appearance of the retinal nerve fiber layer either in monkey^{9,10} or human eyes.^{11,12}

We attempted to identify the initial observable glaucomatous changes in the optic disk and retinal nerve fiber layer in ocular hypertensive eyes in which glaucoma was developing. We also analyzed the mode of subsequent progression of these abnormalities and studied the relationship between nerve fiber layer and optic disk changes.

Patients and Methods

The patients of this study were a subset of a larger patient population consisting of 96 eyes of 96 patients with ocular hypertension. All patients had at least three pairs of optic disk stereophotographs taken during a minimum of five years of follow-up.

For this study we defined ocular hypertension as intraocular pressure of more than 22 mm Hg, normal visual fields (examined with a Friedmann visual field analyzer), normal optic disks, and normal retinal nerve fiber layer. Of the 96 eyes, we therefore excluded 20 eyes (21%) in which, despite the normal visual field and normal appearance of the optic disk, the nerve fiber layer was abnormal in the first pair of photographs. Additionally, 15 of 96 eyes (16%) were excluded because the fundus pigmentation was too light or the photographs were of too poor quality for sequential retinal nerve fiber layer evaluation.

The mean period of follow-up of the remaining 61 patients was 9.7 ± 2.8 years (range, five to 15 years). There were 25 men and 36 women with a mean age of 54.1 years (range, 25 to 75 years). During the follow-up period, the optic

Accepted for publication Dec. 18, 1990.

From the Department of Ophthalmology, University of Oulu, Oulu, Finland. This study was supported by the Sigrid Juselius Foundation, Helsinki, Finland, and the Alcon Research Institute Award. This study was presented in part at the Drance Glaucoma Fellowship Symposium, Vancouver, British Columbia, Canada, March 29, 1990.

Reprint requests to Anja Tuulonen, M.D., Department of Ophthalmology, University of Oulu, SF-90220, Oulu, Finland.

disks had been photographed three to eight times (mean, 4.8 times). The patients had been photographed an average of once every two years. One eye of each patient was analyzed.

Analysis of the photographs of the 61 patients with ocular hypertension showed that 23 patients (38%) (ten men and 13 women) developed typical glaucomatous abnormalities of the optic disk, retinal nerve fiber layer, or both during the follow-up period.

Optic disk stereophotographs (enlarged 13 × 18-cm paper copies) were taken with a Zeiss fundus camera using an Allen stereoseparator with a fixed stereobasis of 2.5 mm. The 30-degree picture angle allowed visibility of a large peripapillary area. We used black-and-white Kodak Panatomic-X film and a green Wratten 58 filter. Since 1982, retinal nerve fiber layer photographs (18 × 23-cm enlarged paper prints) were taken with a wide-angle Canon camera using the same film and a narrow-band blue interference filter with 495-nm wavelength.

The optic disks were evaluated from the stereophotographs by one of us (A.T.) in a masked fashion with no clinical information available. All stereophotographs of a single patient were analyzed in one session without knowledge of the sequence of the photographs to determine whether there was a change in the optic disk and whether the change was localized, generalized, or both. The magnification-corrected neuroretinal rim area, optic disk area, and cup/disk area ratio were measured from the optic disk stereophotographs as previously de-

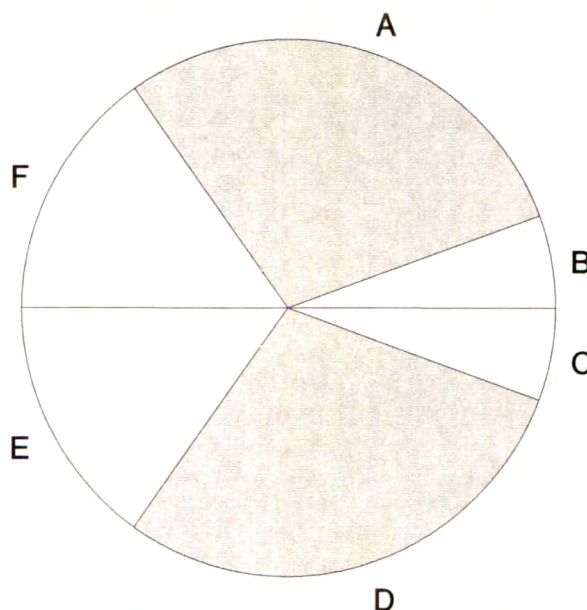


Fig. 1 (Tuulonen and Airaksinen). Optic disk divided into six sectors for location of localized optic disk and retinal nerve fiber layer changes (left eye). Localized optic disk changes were found in sector A in four of ten eyes; in sector D in four of ten eyes; and in both sectors A and D in two of ten eyes. Localized nerve fiber layer changes were found in sector A in six of 11 eyes; in sector D in four of 11 eyes; and in both sectors A and D in one of 11 eyes.

scribed.¹³

The retinal nerve fiber layer was analyzed by one of us (P.J.A.) using the optic disk stereophotographs (27 of 61 eyes [44%]) and retinal nerve fiber layer photographs (34 of 61 eyes [56%]). The analysis was performed in random order in a completely masked fashion with optic disks covered and no clinical information available.

For statistical analysis, differences between group means were tested with *t*-test or analysis of variance. Frequency distributions of discrete variables were tested with Fisher's test of exact probability. The level of statistical significance was chosen as $P < .05$.

Results

Of 61 eyes with ocular hypertension, 23 developed glaucoma (Table). Optic disk hemorrhages were statistically significantly more frequent in eyes with localized notching compared to eyes with generalized enlargement of the optic cup ($P = .004$, Table). Neither the initial intraocular pressure nor the highest intraocular

TABLE
THE TYPE OF INITIAL GLAUCOMATOUS OPTIC DISK
AND RETINAL NERVE FIBER LAYER DAMAGE
IN 23 EYES

TYPE OF DAMAGE	NO.	(%)	HEMOR- RHAGE	NO.	(%)	INTRAOCULAR PRESSURE (MM Hg)		EXFOLI- ATION	NO.	(%)
						INITIAL	HIGHEST			
Optic Disk										
Generalized	10	(44)	2	(20)	25.8±4.9	34.1±6.5	6	(67)		
Local notch	6	(26)	6	(60)	27.2±4.0	29.5±3.2	1	(11)		
Both	4	(17)	2	(20)	26.0±3.7	28.0±3.3	2	(22)		
Pale disk*	3	(13)	0	(0)	23.7±2.3	27.3±3.1	0	(0)		
Retinal Nerve Fiber Layer										
Diffuse	12	(52)	2	(20)	25.4±4.0	30.7±4.1	5	(56)		
Local	7	(31)	5	(50)	28.4±4.9	31.3±7.6	2	(22)		
Both	4	(17)	3	(30)	23.0±4.1	31.0±2.4	2	(22)		

*Pale neuroretinal rim with no change of configuration.

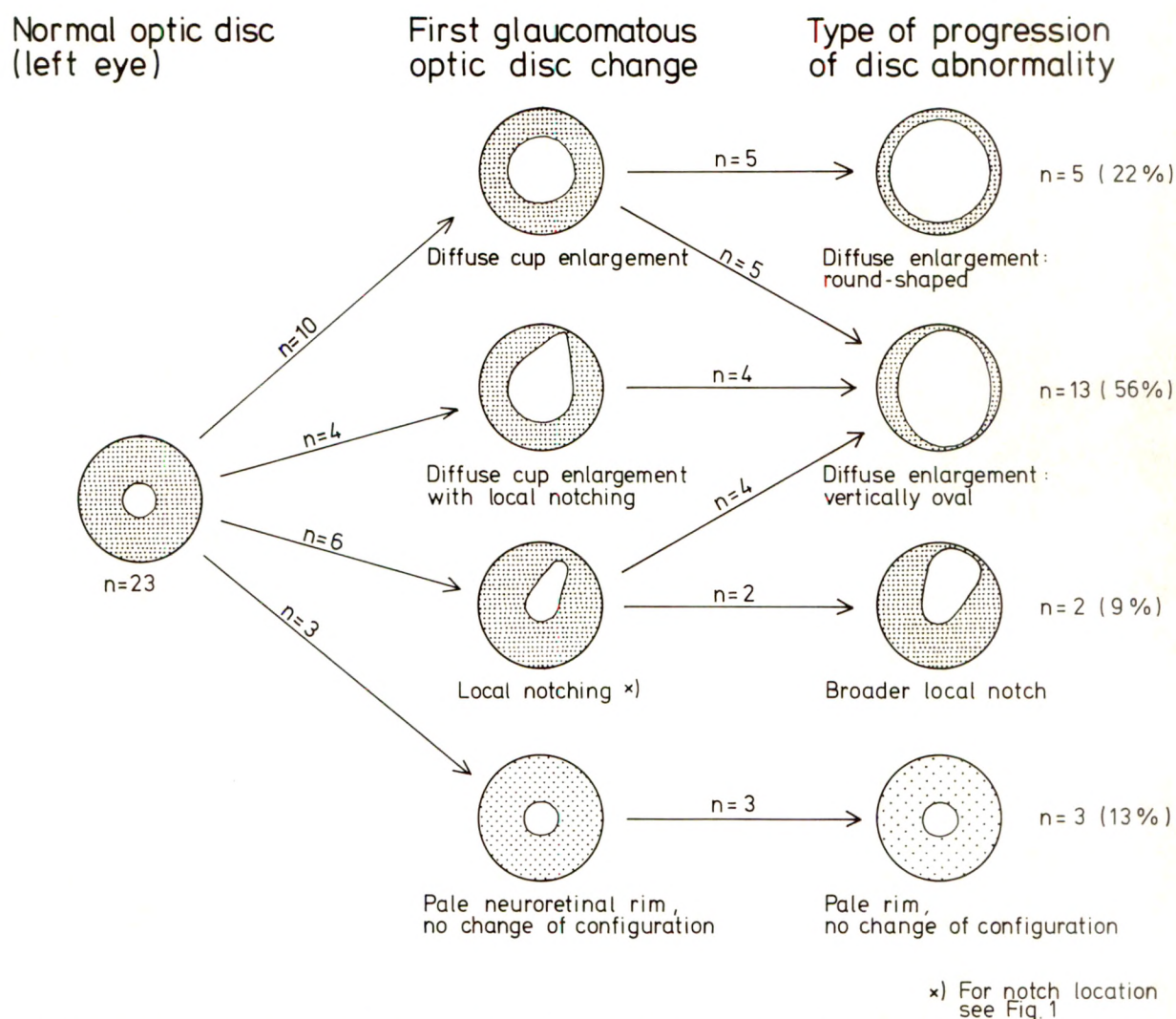


Fig. 2 (Tuulonen and Airaksinen). The type of initial glaucomatous optic disk abnormalities and their progression. All eyes are presented as left eyes.

pressure measured were statistically significantly different between the groups. There were fewer eyes with lens exfoliation in the group with localized damage, but the differences did not reach statistical significance (Table).

The mean initial neuroretinal rim area was smaller ($1.16 \pm 0.11 \text{ mm}^2$) in eyes with localized notching than in eyes with generalized cup enlargement ($1.41 \pm 0.17 \text{ mm}^2$; $P = .009$). There was no statistically significant difference in the mean cup/disk area ratios between eyes with local notching (0.40 ± 0.06) and generalized cup enlargement (0.31 ± 0.11). The optic disks were larger in eyes with diffuse damage ($2.08 \pm 0.29 \text{ mm}^2$) compared to eyes with local damage ($1.92 \pm 0.15 \text{ mm}^2$), but the difference did not reach statistical significance.

Both the first localized optic disk and retinal nerve fiber layer changes were located rather symmetrically in upper and lower temporal regions (Fig. 1). There were no localized changes in the nasal and papillomacular sectors. The type and sequence of progression of the glaucomatous optic disk and retinal nerve fiber layer changes are shown in Figures 2 and 3.

The retinal nerve fiber layer and optic disk changes were concordant in 14 of 23 eyes (61%). In nine eyes, localized disk changes were not associated with localized retinal nerve fiber layer changes and generalized cup enlargement was not associated with diffuse retinal nerve fiber layer thinning, or vice versa.

In 16 of 23 eyes (70%) retinal nerve fiber layer and optic disk abnormalities were observed

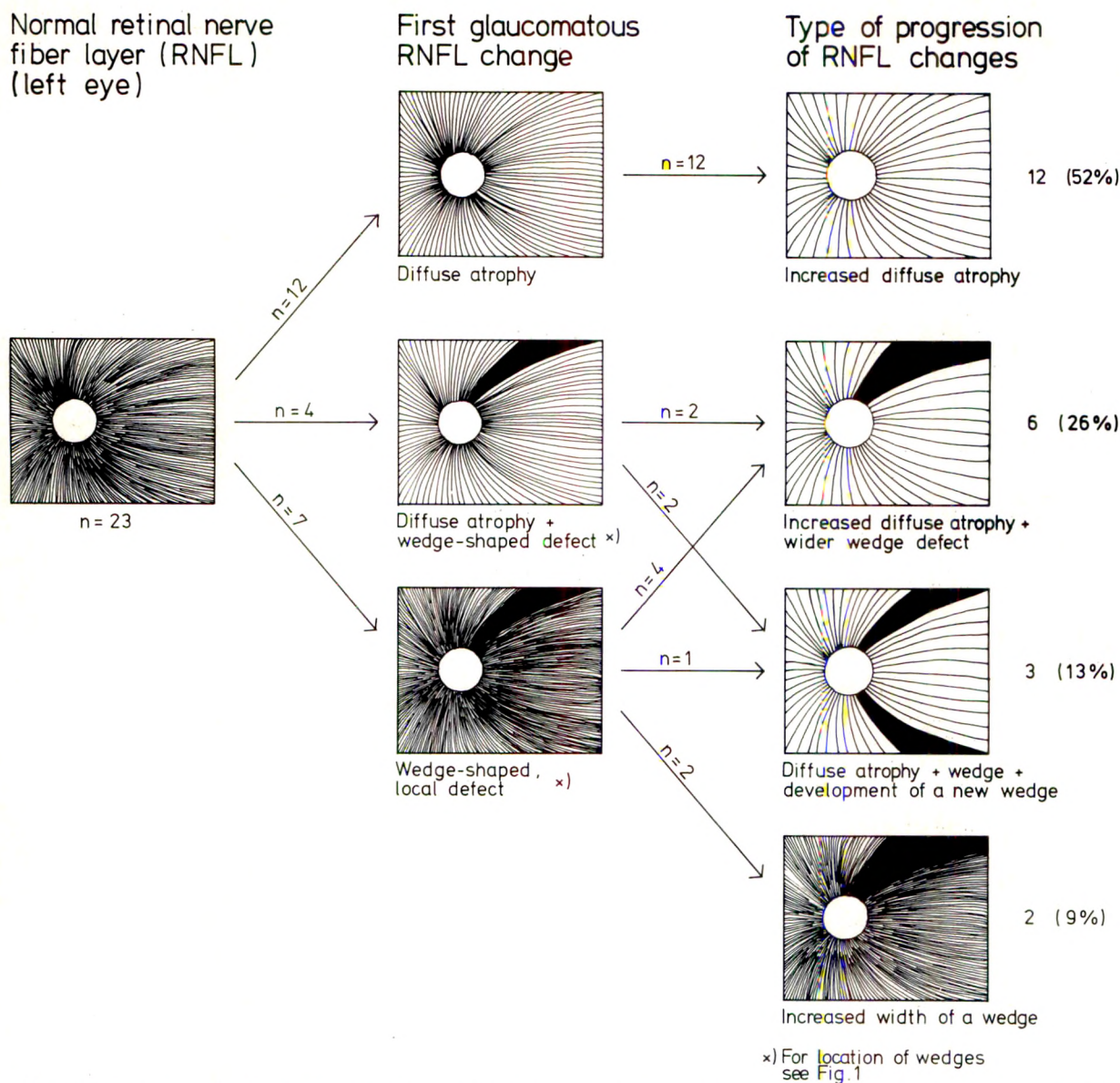


Fig. 3 (Tuulonen and Airaksinen). The type of first glaucomatous retinal nerve fiber layer (RNFL) abnormalities and their progression. All eyes are presented as left eyes.

simultaneously. Four eyes initially had optic disk changes and then had retinal nerve fiber layer changes. Three eyes initially had retinal nerve fiber layer changes and then had optic disk changes.

Discussion

In most eyes the initial sign of glaucomatous abnormality was diffuse damage both in the optic disk (ten of 23 eyes [44%]) and the retinal

nerve fiber layer (12 of 23 eyes [52%]). This finding is in agreement with previous longitudinal⁶ and cross-sectional³ reports on the type of glaucomatous optic disk cupping. Shiose² and Odberg and Riise⁷ have shown local rim notching to be more prevalent. We found localized optic disk damage in ten of 23 patients (44%) and localized retinal nerve fiber layer damage in 11 of 23 patients (48%) alone or in combination with diffuse damage (Table).

There are only a few longitudinal follow-up studies on human eyes dealing with the development of initial retinal nerve fiber layer abnor-

malities. Sommer and associates¹¹ found predominantly local changes in ten patients with initial ocular hypertension, as did Iwata, Nanba, and Abe¹² in a study of five patients with Posner-Schlossman syndrome. Our results are in agreement with a later experimental study of Iwata, Kurosawa, and Sawaguchi⁹ on monkeys in which they found diffuse retinal nerve fiber layer loss alone with no localized changes, in addition to diffuse damage combined with or followed later by a retinal nerve fiber layer wedge. Conversely, Quigley¹⁰ reported retinal nerve fiber layer changes developing and progressing predominantly locally in monkeys.

In 14 of 23 patients (61%), the retinal nerve fiber layer findings were concordant with the optic disk findings, as would be expected. The discrepancies may be because wide-angle retinal nerve fiber layer photography was available only after 1982. This may also influence the higher percentage of diffuse retinal nerve fiber layer loss than we previously reported in a cross-sectional study.¹⁴ A relatively long two-year interval between the photographs may affect the retinal nerve fiber layer and disk changes being found simultaneously in most patients. Our previous studies have indicated that retinal nerve fiber layer damage is seen earlier than optic disk changes.^{15,16} In our study, 20 of 96 eyes (21%) were excluded because of abnormal nerve fiber layer in the presence of normal optic disk and visual field.

Optic disk hemorrhages were more frequent in eyes with local notching (Table), as it has been well established in published reports. From the final disk appearance at the last examination, however, it was not possible to tell which eyes had shown hemorrhages. This is in agreement with our previous results, which indicated that hemorrhages show the location of future damage, but glaucomatous optic disk changes may progress similarly with and without an optic disk hemorrhage.¹⁷

The initial neuroretinal rim area was smaller in eyes with localized notching compared to eyes with generalized cup enlargement, which is possibly because of the difference in disk size. Eyes with localized changes had somewhat smaller disks than eyes with diffuse enlargement of cupping. It is also possible that eyes with localized notching were already generally damaged before the development of local change.³ The normal retinal nerve fiber layer appearance, however, does not support this concept.

Several studies^{1,4,8} have found the type of cupping to be dependent on intraocular pressure level with local notching occurring at moderate intraocular pressure levels and diffuse cup enlargement at higher intraocular pressure levels. In our study, the type of neither glaucomatous optic disk nor retinal nerve fiber layer damage was dependent on intraocular pressure level, which agrees with the findings of Pederson and Anderson.⁶

The interindividual variability in the appearance of initial glaucomatous optic disk and retinal nerve fiber layer damage seems to be large, and the type of future progression is difficult to foretell. Because diffuse changes without localized abnormalities constitute the most common finding, frequent photography is necessary to discover the early changes. The best information is obtained by combining optic disk and wide-angle retinal nerve fiber layer photography. Generalized thinning of the retinal nerve fiber layer, however, is most difficult to judge and requires an experienced observer. Therefore, computerized quantitative retinal nerve fiber layer analysis or laser techniques may offer a solution for reliable diagnostics in early glaucoma.

References

1. Iwata, K.: Topographical analysis on the genesis of glaucomatous cupping. *Glaucoma* 1:16, 1979.
2. Shiose, Y.: "Quantitative disc pattern" as a new parameter for glaucoma screening. *Glaucoma* 1:41, 1979.
3. Jonas, J. B., Gusek, G. C., and Naumann, G. O. H.: Optic disc morphometry in chronic primary open-angle glaucoma. I. Morphometric intrapapillary characteristics. *Graefes Arch. Clin. Exp. Ophthalmol.* 226:522, 1988.
4. Shiose, Y., Ito, T., Amano, M., and Kawase, Y.: Relationship between mode of disc cupping and clinical features in primary open-angle and low-tension glaucoma. *Glaucoma* 9:150, 1987.
5. Sommer, A., Pollack, I., and Maumenee, A. E.: Optic disc parameters and onset of glaucomatous field loss. I. Methods and progressive changes in disc morphology. *Arch. Ophthalmol.* 97:1444, 1979.
6. Pederson, J. E., and Anderson, D. R.: The mode of progressive disc cupping in ocular hypertension and glaucoma. *Arch. Ophthalmol.* 98:490, 1980.
7. Odberg, T., and Riise, D.: Early diagnosis of glaucoma. The value of successive stereophotography of the optic disc. *Acta Ophthalmol.* 63:257, 1985.
8. Nanba, K., and Iwata, K.: Stereochronoscopic study of the optic cup in glaucoma. II. Location and

frequency of optic cup change. *Folia Ophthalmol. Jpn.* 39:361, 1988.

9. Iwata, K., Kurosawa, A., and Sawaguchi, S.: Wedge-shaped retinal nerve fiber layer defects in experimental glaucoma. Preliminary report. *Graefes Arch. Clin. Exp. Ophthalmol.* 223:184, 1985.

10. Quigley, H. A.: Examination of the retinal nerve fiber layer in the recognition of early glaucoma damage. *Trans. Am. Ophthalmol. Soc.* 84:920, 1986.

11. Sommer, A., Miller, N. R., Pollack, I., Maumenee, A. E., and George, T.: The nerve fiber layer in the diagnosis of glaucoma. *Arch. Ophthalmol.* 95:2149, 1977.

12. Iwata, K., Nanba, H., and Abe, H.: Die beginnende Fundusveränderung infolge rezivierender kleiner Krisen beim Posner-Schlossman-Syndrom. Ein Model für das Glaucoma simplex. *Klin. Monatsbl. Augenheilkd.* 180:20, 1982.

13. Airaksinen, P. J., Drance, S. M., and Schulzer,

M.: Neuroretinal rim area in early glaucoma. *Am. J. Ophthalmol.* 99:1, 1985.

14. Airaksinen, P. J., Drance, S. M., Douglas, G. R., Mawson, D. K., and Nieminen, H.: Diffuse and localized nerve fiber loss in glaucoma. *Am. J. Ophthalmol.* 98:566, 1984.

15. Airaksinen, P. J., and Alanko, H. I.: Effect of retinal nerve fibre loss on the optic nerve head configuration in early glaucoma. *Graefes Arch. Clin. Exp. Ophthalmol.* 220:193, 1983.

16. Tuulonen, A., Airaksinen, P. J., Montagna, A., and Nieminen, H.: Screening for glaucoma with a non-mydratic fundus camera. *Acta Ophthalmol.* 68:445, 1990.

17. Tuulonen, A., Takamoto, T., Wu, D.-C., and Schwartz, B.: Optic disk cupping and pallor measurements of patients with a disk hemorrhage. *Am. J. Ophthalmol.* 103:505, 1987.

Intraocular Pressure and the Rate of Visual Field Loss in Chronic Open-Angle Glaucoma

Colm O'Brien, F.R.C.S., Bernard Schwartz, M.D., Takenori Takamoto, Ph.D.,
and Da Ching Wu, Ph.D.

We measured the rate of change of visual field threshold values over time (mean follow-up, 44.9 ± 17.4 months) by trend analysis in 40 eyes of 40 patients with chronic open-angle glaucoma. Twenty-eight eyes had stable visual fields, and two eyes had significant visual field improvement. Ten eyes had significant visual field deterioration and showed a correlation between indices of intraocular pressure (standard error of the mean, $P = .02$; standard deviation, $P = .04$; and range, $P = .05$) and the rate of visual field loss in the superonasal region of the visual field, such that the greater the variation of intraocular pressure the greater the rate of loss. The group losing visual fields had a higher mean visual field threshold value and significantly less optic disk pallor and cupping at the start of the study than the stable visual field group. Thus, a significant rate of visual field loss occurred at an earlier stage of the disease and showed a correlation with intraocular pressure in this stage.

REDUCTION OF INTRAOCULAR PRESSURE by medical and surgical means is the cornerstone of treatment for chronic open-angle glaucoma. The purpose of reducing intraocular pressure is to prevent, or at least slow down, the progres-

sion of visual field loss. In a recent review of 126 eyes with chronic open-angle glaucoma followed up over five years with automated perimetry, 84 (67%) had stable visual fields when intraocular pressure was below 21 mm Hg at all visits.¹ A reduced level of intraocular pressure, however, does not guarantee protection from further damage to the visual field. Progressive visual field loss has been documented in 18% to 40% of patients with chronic open-angle glaucoma despite intraocular pressure in the normal range after filtration surgery,^{2,3} whereas other studies have reported that approximately 75% of patients given treatment continued to lose visual field.^{4,5} Using trend analysis,⁶ we conducted a review to determine the rate of visual field loss over time in eyes with chronic open-angle glaucoma and to observe what relationship the intraocular pressure and other ocular and systemic variables had with the rate of change of the visual field.

Patients and Methods

Patients were included in the study if they fulfilled the following criteria: a diagnosis of high-pressure open-angle glaucoma (that is, intraocular pressure of 21 mm Hg or greater on two separate occasions, open angles by gonioscopy, and characteristic optic nerve and visual field defects); a minimum follow-up period of 20 months; visual acuity of 20/40 or better; five or more automated visual fields on the Octopus 2000R perimeter; and localized visual field defects. We excluded subjects with a history of topical or systemic corticosteroid use.

Using the automated visual field data base of the glaucoma service at our institution,⁷ we identified 40 patients who met the criteria and randomly selected one eye of each patient for further investigation if both eyes qualified for inclusion. The charts of all patients were reviewed, and data on age, sex, race, refractive

Accepted for publication Jan. 7, 1991.

From the Department of Ophthalmology, New England Medical Center Hospitals, and Tufts University School of Medicine, Boston, Massachusetts. This study was supported in part by grants from The Ainsworth Scholarship, The International Glaucoma Association, Research to Prevent Blindness, Inc., and Alcon Research Institute, Fort Worth, Texas. Bernard Schwartz, M.D., has received a copyright for the trend analysis program, which has been assigned to Tufts Medical Center Associates, Boston, Massachusetts.

Reprint requests to Bernard Schwartz, M.D., Department of Ophthalmology, Box 450, New England Medical Center Hospitals, 750 Washington St., Boston, MA 02111.

error, family history of glaucoma, and medical and surgical history were obtained. Measurements of intraocular pressure (Goldmann applanation tonometer) and systemic brachial blood pressure (sphygmomanometer, sitting position) taken during the study period were recorded and used in the analysis. Intraocular pressure readings taken within one month of either laser or intraocular surgery were not included. The study period was defined as the time interval between and including the first and last visual field tests. All patients were given treatment at the time of the initial visual field examination and at all subsequent visits. Details of the type of medical and surgical treatment and the duration of use (calculated on a monthly basis) of all topical and systemic glaucoma medications were gathered from the charts. Visual acuity of all patients at the start and end of the study was obtained, and the mean value was expressed as a ratio.

Visual fields—The visual fields were determined on an Octopus 2000R perimeter. All patients had programs 7 and 33 performed before inclusion in the study, and only program 31 fields were used in the study. The type of visual field defect at the beginning of the study ranged from early localized loss to advanced loss (defined as involvement of three or more quadrants).

The threshold data of the 73 test points were stored in a computerized data base and later retrieved to perform trend analysis,⁶ which had a software package system to assess the direction and rate of change of the visual field over time. A linear regression plot was obtained of the mean threshold value in decibels (dB) for each individual visual field compared with time in months. This was done only after a minimum of five visual field measurements had been performed and then again after each subsequent visual field test. Statistical analysis provided data on the whole visual field, seven selected regions of the visual field, and the 73 individual test points. The seven regions of the visual field were the nasal, temporal, superonasal, superotemporal, inferonasal, inferotemporal, and the central region (Fig. 1).⁸ The printout of the software package included the date and mean threshold value of each visual field, the equation and slope (dB/month) of the regression line (trend analysis slope), and the statistical analysis of the data using both Spearman and Pearson correlations, with the corresponding P values for significance of the slope being different from zero. We used only the

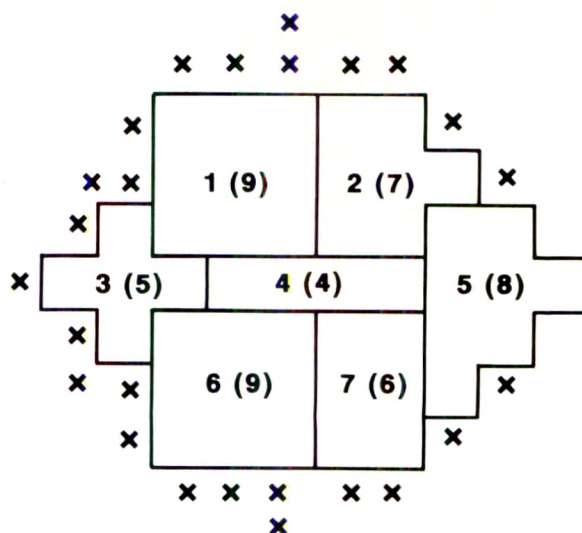


Fig. 1 (O'Brien and associates). Map of the central 30 degrees presented as the left eye. The regions are numbered 1 through 7 with the number of test points per region in parentheses; test points not included in the analysis are marked with an X. Region 1 is superotemporal; region 2 is superonasal; region 3 is temporal; region 4 is central; region 5 is nasal; region 6 is inferotemporal; and region 7 is inferonasal.

Spearman P values to determine statistical significance.

For each patient, the measurements of pupil size, percentage of false-positive and false-negative responses, and the root mean square of each visual field test during the study period were tabulated, and the average value was calculated.

Optic disk and retinal nerve fiber layer measurements—Optic disk cupping and the retinal nerve fiber layer thickness at the optic disk margin were measured by photogrammetry by one of us (T.T.) from sets of simultaneous stereophotographs taken at the same examination with a Donaldson stereofundus camera.^{9,10} Optic disk pallor was measured by one of us (C.O.) using computerized image analysis, with manually applied plan points, from optic disk color photographs taken with a Zeiss fundus camera.¹¹ The area of disk pallor (square millimeters) and cup area (square millimeters) were expressed as ratios of disk area (square millimeters); cup volume (cubic millimeters) and cup depth (millimeters) were expressed as a ratio of disk area (square millimeters); and cup slope was expressed in degrees. Retinal nerve fiber layer thickness (millimeters) was expressed as a ratio of the vertical disk radius (millimeters).

The measurements were performed in a masked fashion as to the visual field status.

The photographs analyzed were taken within six months of the initial visual field at the beginning of the study. The time interval (mean \pm standard deviation) in months between the date of the photograph and the date of the initial visual field was 0.4 ± 2.4 months for optic disk pallor and 1.7 ± 2.7 months for optic disk cupping and retinal nerve fiber layer thickness. The pallor, cupping, and nerve fiber layer measurements were performed twice to assess reproducibility, and the average value was used in the study. Single measurements of two sets of stereophotographs were determined independently for optic disk cupping and nerve fiber layer thickness, and duplicate measurements of a single digitized image were performed independently for disk pallor. The mean \pm standard deviation for percent coefficient of variation (standard deviation/mean \times 100) for differences between duplicate measurements of the total optic disk was $2.8 \pm 2.1\%$ for pallor, $6.0 \pm 3.8\%$ for cup volume, and $4.7 \pm 3.2\%$ for total nerve fiber layer thickness.

Statistical analysis—Nonparametric tests were used to test for a significant difference in the frequency distribution of two populations (Mann-Whitney U) and for correlations between variables (Spearman rank coefficient).¹² Discrete variables were compared with the chi-square test (χ^2 , Fisher's exact test). A probability value (two-tailed test) of less than or equal to .05 was considered significant, and a value of greater than .05 to .10 was considered to be of borderline significance. The statistical tests were performed using BMDP software programs.¹³

Results

Forty eyes of 40 patients were followed up for a mean period of 44.9 ± 17.4 months (range, 20 to 78 months), during which time the mean intraocular pressure was 16.7 ± 2.4 mm Hg. There were 23 men and 17 women; 30 patients were white and ten were black. Twenty-six patients had chronic open-angle glaucoma, ten had the pigmentary dispersion syndrome,¹⁴ and four had pseudoexfoliative glaucoma.¹⁵ The rate of visual field loss of the whole group, as measured by the trend analysis slopes, was -0.029 ± 0.075 dB/month, and the range was from -0.24 to $+0.12$ dB/month. Twenty-two

eyes had negative slopes, and 18 eyes had positive slopes.

Ten of the 22 negative slopes were statistically significant (Spearman $P < .05$; -0.116 ± 0.065 dB/month; range, -0.03 to -0.24 dB/month). Therefore, 25% (ten of 40) of the eyes had a significant rate of visual field deterioration. Two of the 18 positive slopes were significant, $+0.085 \pm 0.035$ dB/month, which indicated that 5% (two of 40) of the eyes had a significant rate of visual field improvement. Thus, 28 of 40 eyes (70%) had nonsignificant slopes and were judged to have stable visual fields (mean, -0.006 ± 0.036 dB/month; range, -0.08 to $+0.12$ dB/month). The mean rate of visual field loss in the group losing visual fields was almost 20 times that of the group with stable visual fields.

We proceeded to compare the stable visual field group with the group losing visual field to identify whether there were other ocular or systemic features that would help to define the groups. For statistical analysis, the two eyes with a significant rate of visual field improvement were pooled with the stable visual field group. A review of the systemic features of both groups showed that there was no significant difference in the age, sex, race, family history of glaucoma, follow-up time, medical history of diabetes mellitus, or in the level of systolic and diastolic blood pressure (Table 1). Seven of the patients with stable and improving visual fields and none of the patients losing visual fields had a history of treated systemic hypertension, but this difference was not significant. The ocular characteristics did not show any significant differences between the groups in the type of glaucoma, refractive error, initial or final visual acuity, or frequency of observed optic disk hemorrhage (Table 1). The groups were not significantly different in the various indices of intraocular pressure. The indices of intraocular pressure used in the analysis refer only to those measurements recorded during the study period. In the group with stable and improving visual fields, seven eyes had argon laser trabeculoplasty, four eyes had cataract surgery, and three eyes had a trabeculectomy before the study began. In the group losing visual fields, four eyes had argon laser trabeculoplasty before the study. One eye from each group had a combined cataract extraction and trabeculectomy before the study.

A comparison of the visual field data is shown in Table 2. The group losing visual fields had a greater mean number of visual field examina-

TABLE 1
SYSTEMIC AND OCULAR CHARACTERISTICS*

	STABLE AND IMPROVING VISUAL FIELDS (N = 30)	LOSING VISUAL FIELDS (N = 10)
Age (years)	60.3 ± 11.2	62.6 ± 15.6
Sex		
Men:Women	19:11	5:5
Race		
White:Black	23:7	8:2
Follow-up (months)	44.6 ± 16.2	46.0 ± 21.5
Family history of glaucoma	6	3
Systemic hypertension	7	0
Diabetes mellitus	4	0
Blood pressure (mm Hg)		
Systolic	132 ± 14	125 ± 11
Diastolic	78 ± 6	75 ± 4
Diagnosis		
Chronic open-angle glaucoma	20	6
Pigment dispersion	8	2
Pseudoexfoliation	2	2
Refractive error (spherical equivalent in diopters)	-0.74 ± 3.4	-0.18 ± 1.6
Visual acuity		
Beginning of study	0.78 ± 0.17	0.76 ± 0.17
End of study	0.75 ± 0.19	0.67 ± 0.13
Disk hemorrhage (eyes)	6	3
Intraocular pressure (mm Hg)		
Mean	16.8 ± 2.5	16.5 ± 1.8
Median	16.5 ± 2.4	16.3 ± 2.0
Standard deviation	3.0 ± 1.2	3.4 ± 1.0
Standard error of the mean	0.77 ± 0.27	0.83 ± 0.48
Peak	23.1 ± 5.4	23.9 ± 4.1
Range	11.0 ± 5.3	12.4 ± 4.2

*Values given are mean ± standard deviation.

tions per eye than the stable and improving visual field group, but this was not significant. At the initial visual field test, the mean threshold value in the total visual field and in all of the regions of the visual field, except the infero-nasal and inferotemporal regions, was higher in the group losing visual fields than in the stable and improving visual field group. This difference was significant in the temporal region ($P = .049$) and was of borderline significance in the superotemporal region ($P = .059$). In the group with stable and improving visual fields, the regions with the lowest mean threshold values at the initial visual field test were the super-onasal, superotemporal, and nasal areas. The nasal and superonasal regions also had the lowest mean threshold values in the group losing visual fields. There were no significant

differences between the groups in the pupil size, percentage of false-positive and false-negative responses, or root mean square values.

The rate of change of the total visual field as well as the various regions of the visual field for the two groups are given in Table 3. Highly significant differences between the two groups in the rate of visual field loss are seen in all the regions and the total visual field. In the group losing visual fields, all seven regions had negative trend analysis slopes. In the group with stable and improving visual fields, positive slopes were seen in the nasal, superonasal, inferonasal, and superotemporal regions. Reviewing the gray-scale printout of the visual field in the ten eyes losing visual fields showed that there was a clear increase in the size and density of preexisting scotomas, with the appearance of new visual field defects in two eyes. There was also a diffuse loss of retinal sensitivity throughout much of that portion that did not show localized loss in these ten eyes. This was confirmed by the regional analysis of trend analysis slopes.

At the beginning of the study, the mean values of the measurements of the optic disk were smaller in the group losing visual fields than the group with stable and improving visual fields (Table 4). Significant differences were seen in cup depth ($P = .009$), cup slope ($P =$

TABLE 2
VISUAL FIELD MEASUREMENTS*

	STABLE AND IMPROVING VISUAL FIELDS (N = 30)	LOSING VISUAL FIELDS (N = 10)
Number of visual fields	11.0 ± 5.3	13.8 ± 6.2
Mean threshold value (dB) of the initial visual field		
Total visual field	13.9 ± 4.9	15.9 ± 3.9
Region		
Nasal	11.3 ± 6.3	12.3 ± 6.6
Temporal	14.6 ± 5.5	18.3 ± 3.9
Superonasal	9.9 ± 7.4	14.2 ± 8.5
Inferonasal	18.0 ± 7.1	16.5 ± 6.6
Superotemporal	10.8 ± 7.2	16.4 ± 5.4
Inferotemporal	18.7 ± 6.1	18.5 ± 6.3
Central	19.9 ± 5.8	21.1 ± 4.8
Pupil size (mm)	2.7 ± 1.1	2.6 ± 1.1
False-positives (%)	4.8 ± 6.5	4.4 ± 4.1
False-negatives (%)	10.1 ± 8.7	9.1 ± 5.5
Root mean square (dB)	3.0 ± 0.8	3.0 ± 0.6

*Values given are mean ± standard deviation.

TABLE 3
RATE OF CHANGE OF VISUAL FIELD THRESHOLDS
OVER TIME (TREND ANALYSIS SLOPES) OF THE TOTAL
VISUAL FIELD AND THE REGIONS OF THE VISUAL
FIELD*

	STABLE AND IMPROVING VISUAL FIELDS (N = 30)(dB/MONTH)	LOSING VISUAL FIELDS (N = 10)(dB/MONTH)	P VALUE
Total visual field	0.000 ± 0.042	-0.116 ± 0.065	.0000
Region			
Nasal	0.016 ± 0.056	-0.149 ± 0.179	.0002
Temporal	-0.012 ± 0.057	-0.178 ± 0.149	.0002
Superonasal	0.021 ± 0.081	-0.134 ± 0.098	.0001
Inferonasal	0.016 ± 0.087	-0.097 ± 0.082	.0001
Superotemporal	0.003 ± 0.071	-0.172 ± 0.123	.0001
Inferotemporal	-0.011 ± 0.071	-0.091 ± 0.079	.0060
Central	-0.003 ± 0.139	-0.121 ± 0.115	.0059

*Values given are mean ± standard deviation.

.002), and disk pallor ($P = .039$), whereas the difference in cup volume was of borderline significance ($P = .080$). The cup area at the retinal surface level and the retinal nerve fiber layer thickness were not significantly different between the two groups.

When the treatment characteristics during the study of these two groups were analyzed, there was no significant difference found in the frequency of either medical or surgical treatment used or in the duration of use of beta-blockers, miotics, epinephrine compounds, and carbonic anhydrase inhibitors (Table 5). The number of eyes treated with argon laser trabeculoplasty or trabeculectomy was not significantly different in the groups.

For both groups, the trend analysis slopes of the total visual field and of each of the seven regions of the visual field were correlated with the intraocular pressure indices (Table 6). In the group losing visual fields, significant correlations (-0.70 to -0.77) were only observed between the trend analysis slopes of the superonasal region of the visual field and the standard deviation ($P = .04$) (Fig. 2), standard error of the mean ($P = .02$), and the range ($P = .05$) of intraocular pressures, and a borderline correlation for the peak pressure ($P = .08$) was observed in the same region. The correlation was such that the greater the intraocular pressure the more negative the trend analysis slope and, therefore, the greater the rate of visual field loss. By contrast, the group with stable and improving visual fields did not have any signifi-

cant correlations between intraocular pressure and the rate of change of the visual field. There was, however, a borderline significant correlation with peak pressure ($P = .07$) in the superonasal region of the visual field.

We did not find any significant correlations between the trend analysis slopes and age, refraction, and systolic or diastolic blood pressure in either group. A significant correlation was seen between the trend analysis slope and the follow-up time in the group losing visual fields ($r_s = .78$, $P = .008$) but not in the group with the stable and improving visual fields ($r_s = -.14$, $P = .48$). The longer the follow-up period, the slower was the rate of visual field loss.

Discussion

One of the main advantages of automated perimetry is the numeric calculation of the retinal light sensitivity. A variety of statistical analyses have been developed to help interpret the numeric data.^{1,6,16-21} As our understanding of the many variables involved in computerized perimetry improves, so too will the statistical analysis of the data, and, most of all, the clinical implications of such analysis. Retinal sensitivity declines with age.²² All visual fields, either normal or glaucomatous, will deteriorate over time, and the longer the follow-up period the greater is the loss.

We identified three groups of patients separated by the statistical significance of the trend analysis of the regression slope of visual field thresholds over time. The mean of the trend analysis slopes of the group (28 eyes) with stable visual fields was -0.006 ± 0.036 dB/month, the mean of the group (ten eyes) losing visual fields was -0.116 ± 0.065 dB/month, and the mean of the two eyes with visual field improvement was 0.085 ± 0.035 dB/month. The mean trend analysis slope of the stable visual field group compares favorably with the reported normal rate of visual field decay with age, -0.58 dB/decade or -0.005 dB/month.²² Two long-term studies,^{4,5} one of ten years and the other of 7.6 years, found that 46 of 63 eyes (73%) and 34 of 45 eyes (76%), respectively, of treated patients with chronic open-angle glaucoma had progressive visual field loss during the follow-up period. Ten of the 40 eyes in our study (25%) had a significant rate of visual field loss, which is similar to results reported by

TABLE 4
OPTIC DISK AND RETINAL NERVE FIBER LAYER MEASUREMENTS AT THE TIME OF THE INITIAL VISUAL FIELD*

	STABLE AND IMPROVING VISUAL FIELDS (N = 30)	LOSING VISUAL FIELDS (N = 10)	P VALUE
Optic disk			
Pallor area (mm ²)/disk area (mm ²)	0.49 ± 0.11	0.40 ± 0.11	.039
Cup volume (mm ³)/disk area (mm ²)	0.29 ± 0.08	0.23 ± 0.09	.080
Cup area (mm ²)/disk area (mm ²)	0.57 ± 0.10	0.53 ± 0.09	.24
Cup depth (mm)/disk area (mm ²)	0.21 ± 0.05	0.16 ± 0.04	.009
Cup slope (degrees)	50.9 ± 8.70	40.0 ± 9.40	.002
Retinal nerve fiber layer thickness (mm)/vertical disk radius (mm)	0.25 ± 0.05	0.24 ± 0.03	.35

*Values given are mean ± standard deviation.

Leydhecker and Gramer,¹ who found that 27 of 126 patients (21%) with open-angle glaucoma had significant progression of visual field loss.

We were unable to identify any systemic features that characterized the eyes with progressive loss of visual field. Seven (23%) of the 30 patients with stable and improving visual fields and none of the ten patients losing visual fields were taking medication for systemic hypertension. Although not statistically significant, this difference suggests a possible beneficial effect of antihypertensive medications on the rate of loss of visual field. Alternatively, the increased systemic blood pressure with systemic hypertension might improve the perfusion pressure at the optic nerve head and help protect the visual field. The mean diastolic blood pressure in the group losing visual fields was lower, but

not significantly lower ($P = .12$), than the group with stable and improving visual fields. A low diastolic blood pressure has been identified as a risk factor for progression of visual field loss in chronic open-angle glaucoma.²³

The ocular features did not help to differentiate the two groups (Table 1). No difference was found between the groups in the different measures of intraocular pressure. The groups, however, were separated by the amount of optic disk damage at the beginning of the study (Table 4), by the relationship between the rate of visual field loss and intraocular pressure (Table 6), and, to a lesser extent, by the mean threshold value at the initial visual field test (Table 2). Although the groups that did and did not show a significant rate of visual field loss differed significantly in the amount of optic disk damage at the beginning of the study,

TABLE 5
CHARACTERISTICS OF TREATMENT DURING STUDY*

	STABLE AND IMPROVING VISUAL FIELDS (N = 30)		LOSING VISUAL FIELDS (N = 10)	
	NO. OF EYES	DURATION (mos)	NO. OF EYES	DURATION (mos)
Beta-blockers	29	36 ± 15	10	42 ± 19
Miotics	27	34 ± 17	9	40 ± 20
Epinephrine compounds	25	29 ± 19	10	29 ± 25
Carbonic anhydrase inhibitors	18	29 ± 18	6	16 ± 20
Argon laser trabeculoplasty	12	—	4	—
Trabeculectomy	2	—	0	—

*Values given are mean ± standard deviation.

TABLE 6
SPEARMAN CORRELATIONS (r_s) BETWEEN THE TREND
ANALYSIS SLOPES OF THE SUPERONASAL REGION
AND INTRAOCULAR PRESSURE

	STABLE AND IMPROVING VISUAL FIELDS (N = 30)		LOSING VISUAL FIELDS (N = 10)	
INDEX OF INTRAOCULAR PRESSURE (MM Hg)	r_s	P VALUE	r_s	P VALUE
Mean	-.24	.20	-.04	.91
Median	-.04	.83	-.04	.91
Standard deviation	-.17	.37	-.71	.04
Standard error of the mean	-.23	.22	-.77	.02
Range	-.22	.24	-.70	.05
Peak	-.33	.07	-.65	.08

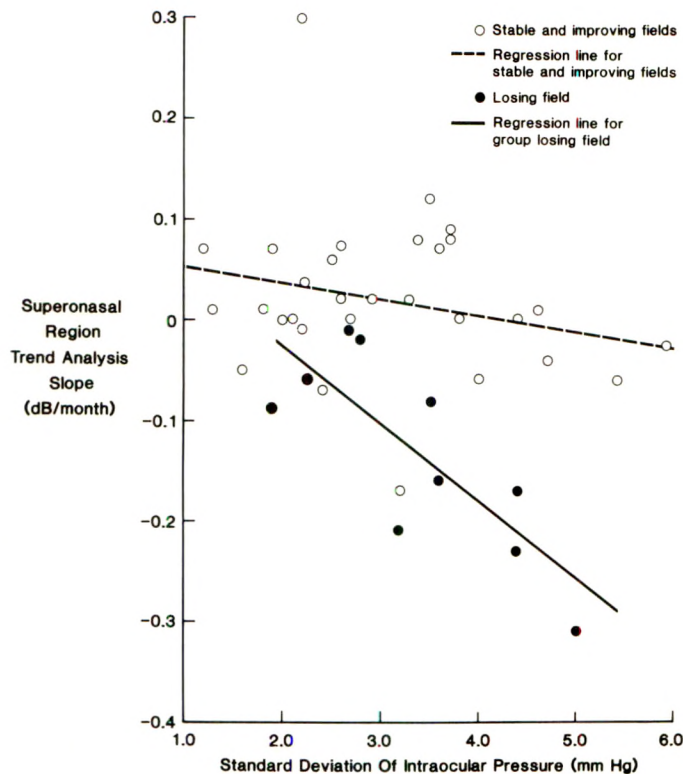


Fig. 2 (O'Brien and associates). Trend analysis slopes of the superonasal region of the visual field plotted against the standard deviation of intraocular pressure. The group losing visual fields shows a statistically significant correlation ($P = .04$).

there was little difference seen in the measurements of retinal nerve fiber layer thickness. This suggests that the retinal nerve fiber layer had already become mostly atrophic at the stage of visual field loss. Therefore, the nerve fiber layer thickness may not be a definitive measure of the stage of the disease once visual field loss has already occurred.

A high mean intraocular pressure has been identified as a risk factor for progression of visual field defects in treated patients with chronic open-angle glaucoma.²³⁻²⁵ Kidd and O'Connor³ reported that nine of 50 patients (18%) with chronic open-angle glaucoma showed progressive visual field loss with a mean intraocular pressure of 15 mm Hg, whereas Hart and Becker⁴ found that 46 of 63 eyes (73%) had further visual field loss with a mean intraocular pressure of 20.4 mm Hg. The findings in our study group fall somewhere in between these two reports, in that ten of 40 eyes (25%) had a significant rate of visual field loss when the mean intraocular pressure was 16.7 mm Hg. The group of patients losing visual fields, however, did not have a significantly different mean intraocular pressure than

the group with stable and improving visual fields (Table 1).

Niesel and Flammer²⁶ demonstrated a significant correlation between the standard deviation of intraocular pressure (calculated on a yearly basis) and progression of visual field loss (measured by planimetry) in patients with ocular hypertension and chronic open-angle glaucoma. Our study showed a significant correlation between some intraocular pressure indices (standard error of the mean, standard deviation, and range) and the rate of visual field loss but only in the group of patients showing a significant rate of visual field loss (Table 6). The relationship was only seen in the superonasal region and suggests that the greater the variation in intraocular pressure the greater the rate of visual field loss.

The superonasal region was the only part of the visual field to show a significant relationship with variation of intraocular pressure in the group of eyes losing visual fields. The nasal and superonasal regions showed the most visual field loss in this group based on the mean threshold values at the beginning of the study (Table 2). Three previous reports have de-

scribed a significant association between intraocular pressure and the loss of nasal field in chronic open-angle glaucoma. Drance, Bryett, and Schulzer²⁷ observed a significant negative regression coefficient between the change in intraocular pressure and the change in visual field thresholds in the inferonasal (central and peripheral) and the superonasal (central) parts of the visual field after surgical reduction of intraocular pressure. Starrita, Fellman, and Lynn²⁸ also noted a significant negative correlation between the change in intraocular pressure and the change in visual field thresholds in the upper and lower nasal field quadrants in eyes with moderate disease (defined as 60% to 80% optic disk cupping) after argon laser trabeculoplasty. Crick and associates²⁹ noted in eyes with chronic open-angle glaucoma that the greatest decrease over time was in the superonasal region of the central visual field.

Other investigators have found no relationship between mean intraocular pressure and rate of visual field loss in the whole visual field as determined by linear regression analysis and automated perimetry. Holmin and Krakau¹⁷ and Krakau³⁰ observed no significant association between mean intraocular pressure less than 22 mm Hg and greater than 21 mm Hg and the regression of visual field thresholds over time in 90 patients with chronic glaucoma followed up for approximately three years with five to 11 central visual fields.

We have observed that the longer the follow-up period, the slower the rate of visual field loss in the group losing visual field. The most likely explanation for this finding is that the longer follow-up time allowed for further intervention in treatment and better control of intraocular pressure and, therefore, a slowing of the rate of visual field loss.

The prevailing concept about the rate of progression of visual field loss in eyes with chronic open-angle glaucoma is that the more advanced the loss of visual field the worse the prognosis^{1,31,32} and the greater the rate of further visual field loss.^{5,18} This is especially true if the intraocular pressure is not controlled adequately.^{33,34} There are observations, however, indicating that, even in advanced cases, reducing the intraocular pressure to low normal levels is associated with preservation of the visual field.³⁵⁻³⁸

Our study showed that the group with the greater rate of visual field loss had less optic nerve damage (significantly less for pallor, cup depth, and slope) and higher initial mean

threshold values (significantly higher for the temporal region) than the stable visual field group. This would indicate that a greater rate of change occurs early in the disease and thus contradicts the traditional viewpoint. Support for this finding is seen in other studies. Holmin and Storr-Paulsen³⁹ noted that the greatest rate of visual field loss occurred in eyes with small- or moderate-size scotomas when linear regression analysis was applied to data obtained with automated perimetry. Also, Schultz and associates²⁰ reported that it was the patients with mild rather than advanced visual field loss who later showed significant progression of visual field loss, again when using automated perimetry. Hart and Becker⁴ described the typical course of progression of visual field loss in eyes with chronic open-angle glaucoma. They stated that once a visual field defect appeared, it would "increase sharply in size and density, following which many years would pass without further progression." Furthermore, Mikelberg and associates⁵ noted that those eyes that showed a curvilinear type of progression had a smaller scotoma mass than those eyes with a linear type of progression. This suggests that the eyes with the smaller scotoma mass and the curvilinear progression were in an earlier stage of disease and were losing visual field at a faster rate than those with the linear type of progression. They found that the mean rates of progression were not significantly different in the linear and curvilinear groups.

If, in chronic open-angle glaucoma, the rate of visual field loss is sensitive to intraocular pressure at an early stage of the disease, then treatment should be aimed at decreasing the intraocular pressure further at an earlier stage of the disease. A primary goal of treatment in glaucoma is to slow the rate of visual field loss, and, therefore, the identification of those patients losing visual field at a significant rate is important. The use of statistical analysis to quantify changes in the threshold values over time provides this type of information.

References

1. Leydhecker, W., and Gramer, E.: Long-term studies of visual field changes by means of computerized perimetry (Octopus 201) in eyes with glaucomatous field defects after normalization of the intraocular pressure. *Int. Ophthalmol.* 13:113, 1989.

2. Werner, E. B., Drance, S. M., and Schulzer, M.: Trabeculectomy and the progression of glaucomatous visual field loss. *Arch. Ophthalmol.* 95:1374, 1977.
3. Kidd, M. N., and O'Connor, M.: Progression of field loss after trabeculectomy. A five-year follow-up. *Br. J. Ophthalmol.* 69:827, 1985.
4. Hart, W. M., Jr., and Becker, B.: The onset and evolution of glaucomatous visual field defects. *Ophthalmology* 89:268, 1982.
5. Mikelberg, F. S., Schulzer, M., Drance, S. M., and Lau, W.: The rate of progression of scotomas in glaucoma. *Am. J. Ophthalmol.* 101:1, 1986.
6. Wu, D. C., Schwartz, B., and Nagin, P.: Trend analyses of automated visual fields. *Doc. Ophthalmol. Proc. Ser.* 49:175, 1986.
7. Wu, D. C., Schwartz, B., Takamoto, T., and Araujo, D.: The use of a database and trend analyses in the clinical management of glaucoma. In Shields, M. B., Pollack, I., and Kolker, A. (eds.): *Proceedings of the American Glaucoma Society*. Thorofare, Slack, 1988, pp. 72-78.
8. Schwartz, B., and Nagin, P.: Probability maps for evaluating automated visual fields. In Heijl, A., and Greve, E. L. (eds.): *Proceedings of the 6th International Visual Field Symposium*. Dordrecht, Dr. W. Junk, 1985, pp. 39-48.
9. Takamoto, T., and Schwartz, B.: Reproducibility of photogrammetric optic disk cup measurements. *Invest. Ophthalmol. Vis. Sci.* 26:814, 1985.
10. ———: Photogrammetric measurements of nerve fiber layer thickness. *Ophthalmology* 96:1315, 1989.
11. Nagin, P., Schwartz, B., and Namba, K.: The reproducibility of computerized boundary analysis for measuring optic disc pallor in the normal optic disc. *Ophthalmology* 92:243, 1985.
12. Siegel, S.: *Nonparametric Statistics for the Behavioral Sciences*. New York, McGraw-Hill, 1956.
13. Dixon, W. J., Brown, M. B., Engelman, L., Hill, M. A., and Jennrich, R. I.: *BMDP Statistical Software*. Berkeley, University of California Press, 1988.
14. Campbell, D. G.: Pigmentary dispersion and glaucoma. A new theory. *Arch. Ophthalmol.* 97:1667, 1979.
15. Prince, A. M., and Ritch, R.: Clinical signs of the pseudoexfoliation syndrome. *Ophthalmology* 93:803, 1986.
16. Gloor, B., Schmied, U., and Fassler, A.: Changes of glaucomatous field defects, analysis of Octopus fields with programme Delta. *Doc. Ophthalmol. Proc. Ser.* 26:11, 1981.
17. Holmin, C., and Krakau, C. E. T.: Regression analysis of the central visual field in chronic glaucoma cases. A follow-up study using automated perimetry. *Acta Ophthalmol.* 60:267, 1982.
18. Wilson, R., Walker, A. M., Dueker, D. K., and Crick, R. P.: Risk factors for rate of progression of glaucomatous visual field loss. A computer-based analysis. *Arch. Ophthalmol.* 100:737, 1982.
19. Spaeth, G. L.: The effect of change in intraocular pressure on the natural history of glaucoma. Lowering intraocular pressure in glaucoma can result in improvement of visual fields. *Trans. Ophthalmol. Soc. U.K.* 104:256, 1985.
20. Schultz, J. S., Werner, E. B., Krupin, T., Bishop, K. I., and Koelle, J.: Intraocular pressure and visual field defects after argon laser trabeculoplasty in chronic open-angle glaucoma. *Ophthalmology* 94:553, 1987.
21. Heijl, A., Lindgren, G., and Olsson, J.: A package for the statistical analysis of visual fields. *Doc. Ophthalmol. Proc. Ser.* 49:153, 1987.
22. Haas, A., Flammer, J., and Schneider, U.: Influence of age on the visual fields of normal subjects. *Arch. Ophthalmol.* 101:199, 1986.
23. Richler, M., Werner, E. B., and Thomas, D.: Risk factors for progression of visual field defects in medically treated patients with glaucoma. *Can. J. Ophthalmol.* 17:245, 1982.
24. Crick, R. P., Vogel, R., Newson, R., Hunt, B., Shipley, M., Blackmore, H., and Bulpitt, C.: Relationship between intraocular pressure and visual field progress in chronic simple glaucoma and ocular hypertension. *Glaucoma* 7:208, 1985.
25. Vogel, R., Crick, R. P., Newson, R. B., Shipley, M., Blackmore, H., and Bulpitt, C. J.: Association between intraocular pressure and loss of visual field in chronic simple glaucoma. *Br. J. Ophthalmol.* 74:3, 1990.
26. Niesel, P., and Flammer, J.: Correlations between intraocular pressure, visual field and visual acuity, based on 11 years of observations of treated chronic glaucomas. *Int. Ophthalmol.* 3:31, 1980.
27. Drance, S. M., Bryett, J., and Schulzer, M.: The effects of surgical pressure reduction on the glaucomatous field. *Doc. Ophthalmol. Proc. Ser.* 14:153, 1977.
28. Starrita, R. J., Fellman, R. L., and Lynn, J. R.: Correlation of intraocular pressure and visual field after argon laser trabeculoplasty. *Doc. Ophthalmol. Proc. Ser.* 49:377, 1987.
29. Crick, R. P., Vogel, R., Newson, R. B., Shipley, M. J., Blackmore, H., Palmer, A., and Bulpitt, C. J.: The visual field in chronic simple glaucoma and ocular hypertension. Its character, progress, relationship to the level of intraocular pressure and response to treatment. *Eye* 3:536, 1989.
30. Krakau, C. E. T.: Visual field decay in chronic glaucoma. In Krieglstein, G. K., and Leydhecker, W. (eds.): *Glaucoma Update II*. New York, Springer-Verlag, 1983, pp. 123-132.
31. Kronfeld, P. C., and McGarry, H. I.: Five year follow-up of glaucomas. *JAMA* 136:957, 1948.
32. Riise, P.: Long-term prognosis in glaucoma surgery. *Am. J. Ophthalmol.* 45:807, 1958.
33. Chandler, P. A.: Long-term results in glaucoma therapy. *Am. J. Ophthalmol.* 49:221, 1960.
34. Grant, W. M., and Burke, J. F., Jr.: Why do some people go blind from glaucoma? *Ophthalmology* 89:991, 1982.

35. Kolker, A. E.: Visual prognosis in advanced glaucoma. A comparison of medical and surgical therapy for retention of vision in 101 eyes with advanced glaucoma. *Trans. Am. Ophthalmol. Soc.* 75:539, 1977.

36. Quigley, H. A., and Maumenee, A. E.: Long-term follow-up of treated open-angle glaucoma. *Am. J. Ophthalmol.* 87:519, 1979.

37. Abedin, S., Simmons, R. J., and Grant, W. M.:

Progressive low-tension glaucoma. Treatment to stop glaucomatous cupping and field loss when these progress despite normal intraocular pressure. *Ophthalmology* 89:1, 1982.

38. Odberg, T.: Visual field prognosis in advanced glaucoma. *Acta Ophthalmol.* 65:27, 1987.

39. Holmin, C., and Storr-Paulsen, A.: The visual field after trabeculectomy. A follow-up study using computerized perimetry. *Acta Ophthalmol.* 62:230, 1984.

OPHTHALMIC MINIATURE

Nor were they bothered by the fast firing of my strobe, which was activated for less duration than a bolt of lightning. One night, however, the celluloid fell off my focusing light, and the beavers were bathed in its white beam. To my surprise, they did not seem at all disturbed by this.

I speculated that the animals had probably become habituated to the headlights of passing automobiles and, from then on, I left my focusing light uncovered. As a result, I discovered something else: when caught in a beam of light, a beaver's eyes do not look like two burning coals. This was significant information, and there could be only one explanation for it: the beaver's retinae do not contain the light-gathering crystal called *tapetum lucidum*.

Hope Ryden, *Lily Pond. Four Years with a Family of Beavers*
New York, William Morrow and Company, pp. 44 and 45

Identification, Prevention, and Treatment of Silicone Oil Pupillary Block After an Inferior Iridectomy

Elisha Bartov, M.D., Ruth Huna, M.D., Isaac Ashkenazi, M.D.,
Shlomo Melamed, M.D., Isaac Gutman, M.D., Nava Naveh, M.D.,
and Giora Treister, M.D.

We treated two patients in whom silicone oil pupillary block developed despite a patent inferior iridectomy. The clinical characteristics of this complication were a deep anterior chamber, specular reflexes from the iris surface, identification by biomicroscopy of aqueous trapped inferiorly in the vitreous cavity, and no convection currents in the anterior chamber. This complication may be prevented by early face-down positioning of the patient after the operation, and the avoidance of large, centrally located, inferior iridectomies. We recommend that the iridectomy be placed peripherally no larger than 2 mm and propose a new technique for breaking the silicone oil block, which was clearly successful in one of the patients.

OPTHALMIC USE of silicone oil in complicated retinal detachment surgery is common.^{1,2} Silicone oil–corneal endothelial touch was a common complication of this operation.^{3,4} The introduction by Ando³ and Beekhuis and associates⁵ of the inferior iridectomy has greatly reduced the rate of this complication. There are instances, however, when silicone oil pupillary block develops despite an inferior iridectomy. We treated two patients with this complication. These patients share several important characteristics whose identification is essential for diagnosing this complication correctly. We propose a treatment technique that successfully

abolished the silicone block in one patient and possibly in the other.

Case Reports

Case 1

A 60-year-old man underwent a vitrectomy, membranectomy, intraocular cryopexy, silicone oil injection, removal of a posterior chamber intraocular lens, and an inferior peripheral iridectomy in the left eye for total tractional retinal detachment of three months' duration. Pseudophakic rhegmatogenous retinal detachment had been successfully treated with a buckling operation 20 months previously. The day after the last operation, intraocular pressure was 50 mm Hg, and the anterior chamber was deep and completely filled with silicone. The retina was attached. The patient was taking timolol 0.5% twice daily, 250 mg of acetazolamide four times daily, and intravenous mannitol. Indirect biomicroscopy with a +90-diopter lens showed aqueous trapped inferiorly below the silicone bubble in the vitreous cavity. Prone positioning of the patient for three days did not result in silicone oil retraction from the anterior chamber.

On the third postoperative day, a maneuver to cause migration of the trapped aqueous from the vitreous cavity to the anterior chamber was performed. This was done by pressing the tip of a glass tube on the cornea with the patient in a prone position and suddenly releasing the pressure. After this procedure, the anterior chamber filled with aqueous, and the silicone bubble retracted to the vitreous cavity with the anterior surface at the level of the pupil. Intraocular pressure decreased to 30 mm Hg with a regimen of timolol only. During the next 11 months, intraocular pressure remained 18 to 24 mm Hg

Accepted for publication Jan. 2, 1991.

From the Goldschleger Eye Institute, Chaim Sheba Medical Center, Tel-Hashomer, Israel.

Reprint requests to Elisha Bartov, M.D., Department of Ophthalmology, Chaim Sheba Medical Center, Tel-Hashomer, 52621 Israel.

with timolol treatment, and the retina remained attached.

Case 2

A 57-year-old man had noninsulin-dependent diabetes mellitus of 19 years' duration, bilateral proliferative diabetic retinopathy, and rubeosis iridis in the right eye. The patient was also pseudophakic in the right eye after extracapsular cataract extraction and a posterior chamber intraocular lens implantation. Because of tractional retinal detachment, he underwent removal of the intraocular lens and posterior capsule, vitrectomy, membranectomy, silicone oil injection, and an inferior peripheral iridectomy in the right eye.

On the third postoperative day, intraocular pressure increased to 32 mm Hg, and the anterior chamber was deep and completely filled with silicone oil. The inferior iridectomy was patent but partially covered with a fibrin membrane. The patient was given timolol 0.5% twice daily and 250 mg of acetazolamide daily and remained prone at all times. On the fifth postoperative day, an attempt to press the cornea with a glass tube did not result in an immediate break in the silicone pupillary block. The patient remained prone, and the next morning the silicone face was seen posterior to the pupil, and intraocular pressure was 26 mm Hg. During the next ten months of follow-up, intraocular pressure remained at 20 mm Hg with timolol 0.5% twice daily and 250 mg of acetazolamide four times daily. The block did not recur.

Discussion

At the conclusion of silicone oil injection in aphakic eyes with the patient in a supine position, the silicone oil bubble frequently floats up and fills the anterior chamber. Concurrently, aqueous in the anterior chamber is filtered out of the angle or gravitates inferiorly through the inferior iridectomy. A large, centrally located, inferior peripheral iridectomy may allow contact between the surface silicone oil bubble in the anterior chamber and the oil bubble in the vitreous cavity. After such contact, the surfaces of the silicone bubbles may unite and create a continuation of silicone oil through the inferior iridectomy, in addition to the one through the

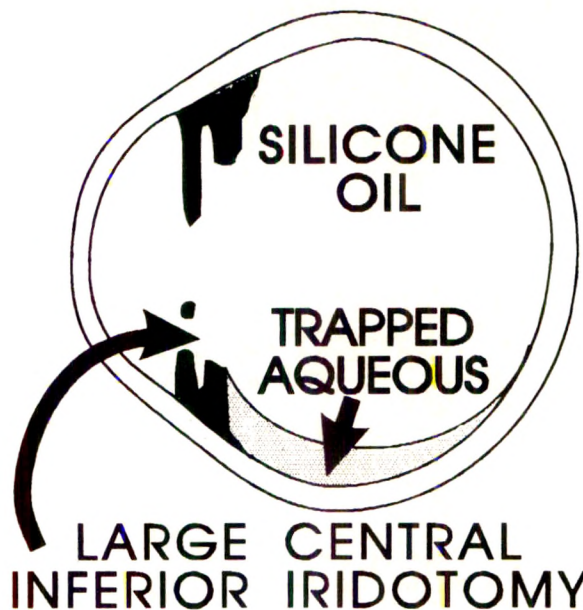


Fig. 1 (Bartov and associates). Continuity of silicone oil through the pupil and through the inferior iridectomy.

pupil (Fig. 1). At these relatively narrow openings, the high surface tension of the silicone oil prevents the passage of aqueous from the posterior to the anterior chamber. Any aqueous that is produced remains trapped posteriorly and inferiorly in the vitreous cavity. The tension of the silicone oil in the margins of the openings serves as an obstruction, which does not permit the aqueous to percolate forward. This condition is stable and does not change even when the patient is placed face down.

Slit-lamp identification of the complete filling of the anterior chamber with silicone oil and its continuity with the silicone oil in the vitreous cavity, both through the pupil and the inferior iridectomy, may not be easy. Careful examination may be necessary. An extremely deep anterior chamber, resulting from the tendency of the silicone oil in the anterior chamber to become spherical and thus push the iris backward, may be noted. This contrasts with a more shallow anterior chamber when the silicone oil anterior surface is where it should optimally be at the pupillary plane.

By illuminating the anterior iris surface from specific directions, a distinct specular reflex may be seen. This results from tight approximation of the silicone oil in the anterior chamber

with the anterior iris surface. If the posterior surface of the anterior chamber silicone oil is not tight against the surface of the iris, this specular reflection cannot be obtained. This is similar to the light reflex from the retinal surface when silicone oil completely fills the vitreous cavity and is positioned tightly against the retina.

Aqueous trapped inferiorly in the vitreous cavity can usually be identified by indirect ophthalmoscopy or biomicroscopy. In such a case, the inferior surface of the silicone oil bubble in the vitreous cavity is seen separated from the retina; that is, there is aqueous trapped underneath the silicone oil bubble.

By using narrow slit-beam illumination, impurities in the silicone oil can be observed in the anterior chamber, which remain stationary and do not follow convection currents as cells in anterior chamber aqueous usually do.

As demonstrated in Cases 1 and 2, treatment of this condition is sometimes possible by breaking the connection between the silicone

oil in the anterior chamber and the vitreous cavity through the inferior iridectomy. This is done by placing the patient in a face-down position, pushing slowly upward on the central cornea, and quickly releasing the pressure (Fig. 2). We believe the pressure on the cornea and the sudden release cause a break in the continuity of the silicone at the iridectomy level. This may be similar to shaking an ampule for injection to cause superiorly trapped fluid to come down. If this maneuver is successful, aqueous is seen to fill the anterior chamber, the silicone oil surface moves back and loses its approximation to the corneal endothelium, and there is aqueous continuity between the anterior and posterior chambers through the inferior iridectomy. As demonstrated in Case 2, the resolution of the pupillary block after the maneuver may not be immediate but may take several hours. If this maneuver does not result in cessation of the silicone oil pupillary block within approximately one day, however, we recommend that excess silicone oil be removed. It is not clear why in one patient resolution of the block after the maneuver was immediate, whereas in the other patient it was delayed. This can possibly be explained by early tissue swelling, which displaced the silicone anteriorly and allowed little place for intraocular collection of aqueous. Later, when the tissue swelling subsided, the increased amount of intraocular aqueous with the patient prone may have allowed the silicone oil block to break.

Preventive measures may significantly reduce the occurrence of this complication. When performing an inferior iridectomy during vitrectomy and silicone oil injection surgery or postoperatively by laser, the surgeon should attempt to make the iridectomy as peripheral as possible. Excessively large iridectomies (larger than 2 mm in diameter) should be avoided, since in such a case the curved surface of silicone oil on the two sides of the iris can come into contact and then unify, which causes a silicone oil block of the inferior iridectomy. If a large, centrally located iridectomy was created inadvertently, however, we suggest that another smaller and more peripheral additional iridectomy be performed. The smaller and more peripheral additional iridectomy will maintain a route for aqueous to enter the anterior chamber and, thus, prevent the stabilization of the silicone oil pupillary block. Additionally, the patient should be instructed to lie face down as

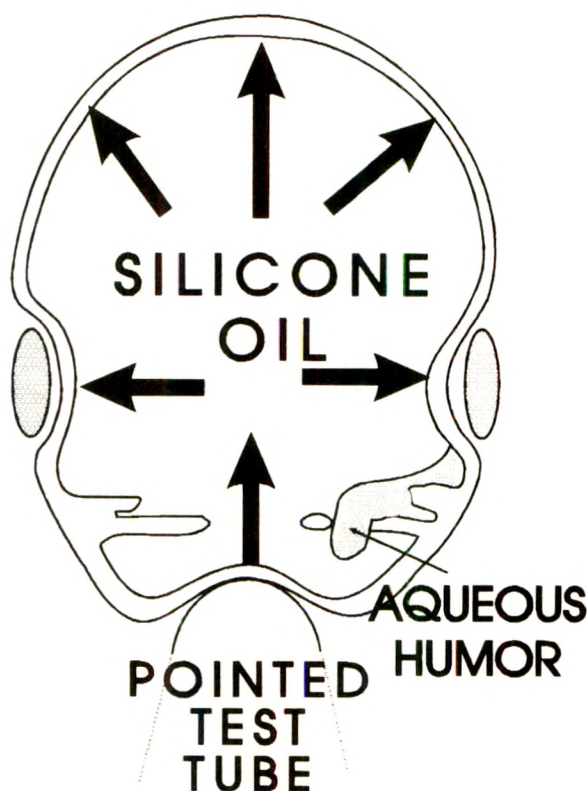


Fig. 2 (Bartov and associates). Maneuver proposed for breaking the silicone oil pupillary block.

soon as possible after the operation, since this complication can only develop while the patient is in a supine position. Early face-down position may prevent and even reverse the development of the complication.

References

1. Grey, R. H. B., and Leaver, P. K.: Silicone oil in the treatment of massive preretinal retraction. I. Results in 105 eyes. *Br. J. Ophthalmol.* 63:355, 1979.
2. Lucke, K. H., Foerster, M. H., and Laqua, H.:

Long-term results of vitrectomy and silicone oil in 500 cases of complicated retinal detachment. *Am. J. Ophthalmol.* 104:624, 1987.

3. Ando, F.: Intraocular hypertension resulting from pupillary block by silicone oil. *Am. J. Ophthalmol.* 99:87, 1985.

4. Zborowski-Gutman, L., Treister, G., Naveh, N., Chen, V., and Blumenthal, M.: Acute glaucoma following vitrectomy and silicone oil injection. *Br. J. Ophthalmol.* 71:903, 1987.

5. Beekhuis, W. H., Ando, F., Zivojnovic, R., Mertens, D. A. E., and Peperkamp, E.: Basal iridectomy at 6 o'clock in the aphakic eye treated with silicone oil. Prevention of keratopathy and secondary glaucoma. *Br. J. Ophthalmol.* 71:197, 1987.

OPHTHALMIC MINIATURE

But Dan McBride, when Randy went to meet him in Berkeley, turned out to be totally blind—a twenty-seven-year-old kid who had somehow actually gone through Harvard Law School without any vision, in these times when disabled people were supposed to get an even break. His two eyes, wide and pure with the clarity of never having seen anything, seemed to be focused on that abstract point in the distance where parallel lines theoretically meet.

Louis B. Jones, *Ordinary Money*
New York, Viking, 1990, p. 192

The Effects of Nd:YAG Laser Iridotomy on the Corneal Endothelium

William C. Panek, M.D., David A. Lee, M.D., and Robert E. Christensen, M.D.

We studied 18 eyes of 18 patients undergoing Nd:YAG laser peripheral iridotomy for occludable anterior chamber angles. A Q-switched laser was used for all treatments. Preoperative and postoperative pachymetry and corneal endothelial cell counts were obtained centrally, in the nontreated superonasal quadrant, and in the treated superotemporal quadrant. No significant differences were found between preoperative and postoperative corneal thickness at any site. A small decrease in endothelial cell count (95 cells/mm²) at the treated site was statistically significant ($P = .04$).

PULSED ND:YAG LASER IRIDOTOMY is a commonly used, effective treatment for angle-closure glaucoma. Studies indicate that this procedure, which uses photodisruption rather than heat absorption to create a patent iridotomy, is safe and without significant long-term complications.

As with the argon laser, animal and human studies have shown that corneal changes can occur after Nd:YAG iridotomy. These changes include focal corneal opacities,^{1,4} linear cracks in Descemet's membrane,¹ focal denuding of the corneal endothelium,^{1,5} and cellular pleomorphism.⁵ The clinical importance of such corneal damage secondary to the Nd:YAG laser is unclear. No studies have demonstrated resultant permanent corneal edema.

We used specular microscopy and pachyme-

try to measure endothelial cell density and corneal thickness in treated and untreated quadrants of the cornea, before and after Nd:YAG laser iridotomy.

Patients and Methods

Eighteen patients (23 eyes) were enrolled in this study. All eyes had clinically determined narrow, occludable anterior chamber angles by gonioscopy. Each eye either had chronic angle-closure glaucoma or was the fellow eye of an eye that had a previous angle-closure glaucoma attack. Eyes with preexisting corneal disease or with a history of angle-closure attack were excluded from the study. A complete ocular examination was performed on each patient, including slit-lamp biomicroscopy, tonometry, gonioscopy, ophthalmoscopy, and visual field examination.

All eyes underwent Nd:YAG laser iridotomy in the superotemporal quadrant of the peripheral iris. All procedures were performed at our institution. Before the laser treatment, a drop of proparacaine hydrochloride 0.5% was instilled, and an Abraham YAG gonioscopes with methylcellulose was placed on the corneal surface. The iridotomies were all performed using a Q-switched laser. The number of shots varied from one to 92 with a mean of 19 (standard deviation, 23). The number of pulses per burst varied from one to three. Power setting for the iridotomies varied from 3.1 to 6.8 mJ. There were no significant complications during the laser procedure in any case.

Before laser iridotomy, corneal endothelial cell counts and pachymetry were obtained centrally, in the treated superotemporal quadrant, and in the untreated superonasal quadrant. A specular microscope was used in conjunction with a video recording system. After careful focusing, the cells were recorded and counted from the video screen. Pachymetry was per-

Accepted for publication Jan. 9, 1991.

From the Jules Stein Eye Institute, UCLA Medical Center, Los Angeles, California. This study was supported in part by National Institutes of Health grants EY07701 and EY00331, Research to Prevent Blindness, Inc., Lucille Ellis Simon Glaucoma Research Fund, and the Karl Kirchgessner Foundation.

Reprint requests to William C. Panek, M.D., Glaucoma Division, 100 Stein Plaza, Los Angeles, CA 90024-7004.

formed with the same machine. The measurements were repeated in the same locations within one to eight weeks after the iridotomy.

Comparisons of corneal status were made before and after laser treatment in all measured locations. To eliminate bias, if both eyes underwent iridotomy, one was randomly selected for inclusion in the statistical analysis, which left a total of 18 eyes for study. Student's paired *t*-test and the paired Wilcoxon test were used. A level of $P < .05$ was considered statistically significant.

Results

The normal endothelial cell count according to the criteria of our laboratory is 2,000 to 4,000 cells/mm². All eyes in this study had cell counts that were within what we considered to be a normal range. No significant differences were found between preoperative and postoperative corneal thickness at any location (Table). A small decrease in corneal endothelial cell count postoperatively at the treated site (95 cells/mm²) was statistically significant ($P = .04$). No significant postoperative difference in cell count was found at either of the two nontreated sites.

The 95% confidence interval for the mean change score (preoperative minus postopera-

tive) of the cell count in the treated superotemporal quadrant was -185 to -3 cells/mm² given the sample size of 18 eyes.⁶

Discussion

The Nd:YAG laser has been used safely and effectively to create a peripheral iridotomy in the treatment of angle-closure glaucoma. Because the Nd:YAG laser functions independently of the level of tissue pigmentation, it has been found to be particularly helpful in treating lightly pigmented irides that would be difficult to penetrate with the argon laser.

Clinical studies indicate that the minimal complication rates seen with the Nd:YAG laser compare favorably with those resulting from the argon laser. Complications include a measurable breakdown of the blood-aqueous barrier in the anterior segment, transient acute increase of intraocular pressure, bleeding from the iridotomy site, self-limited injury to the anterior lens capsule and nonprogressive corneal changes.¹ With excessive energy levels, capsular and zonular complications have been reported.⁷

Corneal epithelial burns are seen rarely in Nd:YAG laser iridotomy when compared to argon laser iridotomy. This is caused in part by a reduction in energy absorption in the corneal tissues with the Nd:YAG laser. The total energy requirement for Nd:YAG laser iridotomy is significantly less than that required for argon laser (8 to 200 mJ compared with 5,000 to 50,000 mJ).¹

Damage to the cornea in Nd:YAG iridotomy may occur as a result of plasma formation propagating toward the laser delivery source and subsequently toward the corneal endothelium.⁸ Local denuding of the corneal endothelium can occur when the laser is focused too close to the endothelial surface.⁸ Nonprogressive cracks at the level of Descemet's membrane have been described directly overlying the iridotomy site, which probably also represent concussive changes secondary to plasma formation.¹ The clinical significance of these corneal changes seen after Nd:YAG laser iridotomy is unclear. Animal^{5,9} and human^{2,5} studies have produced conflicting evidence regarding the short-term changes. No studies have shown a significant long-term, clinically significant problem.

Dragon and associates⁹ used scanning elec-

TABLE
PREOPERATIVE AND POSTOPERATIVE PACHYMETRY
AND ENDOTHELIAL CELL DENSITY OF 18 EYES

	CORNEAL THICKNESS (MM)	CELL DENSITY (MM ²)
	MEAN \pm S.D.	MEAN \pm S.D.
Untreated central site		
Preoperative	0.54 \pm 0.04	2478 \pm 282
Postoperative	0.54 \pm 0.04	2472 \pm 272
Difference	0.00 \pm 0.03	-6 \pm 180
Treated superotemporal site		
Preoperative	0.56 \pm 0.04	2517 \pm 376
Postoperative	0.57 \pm 0.04	2422 \pm 292
Difference	0.01 \pm 0.02	-95 \pm 183
Untreated superonasal site		
Preoperative	0.56 \pm 0.04	2467 \pm 351
Postoperative	0.56 \pm 0.04	2378 \pm 330
Difference	0.00 \pm 0.02	-89 \pm 237

tron microscopy to study the corneal endothelium overlying Nd:YAG laser iridotomy sites in four cynomolgus monkeys. They found no significant endothelial cell loss or pleomorphism when compared to adjacent untreated areas. Kerr Muir and Sherrard,⁵ however, did find irreversible changes in the corneal endothelium of fresh rabbit eyes after Nd:YAG laser iridotomy using scanning electron microscopy. They believed that the corneal changes were related to the quantity of power delivered, the delivery mode, the number of laser bursts, and the target tissue-to-endothelium distance.

Human clinical studies have shown that mild nonprogressive corneal changes occur frequently. Schwartz and associates² found corneal changes in seven of 182 (4%) treated eyes. Robin and Pollack⁴ found focal, discrete, nonprogressive endothelial changes above the iridotomy site in six of 33 (18%) treated eyes. In an earlier study, they³ had shown a 35% incidence of focal, nonprogressive corneal opacities overlying the Nd:YAG iridotomy site of 20 eyes compared with a 25% incidence of similar opacities overlying the argon iridotomy site of 20 fellow eyes. A significant drop in central endothelial cell count was found in eyes after argon laser iridotomy (8%) compared to Nd:YAG laser (0%) in the same study. The mean preoperative endothelial counts were $2,898 \pm 498$ and $2,877 \pm 475$ in the argon- and Nd:YAG-treated eyes, respectively. The mean postoperative counts were $2,585 \pm 476$ and $2,711 \pm 445$, respectively.

Previously we reported that no significant corneal endothelial cell loss or increased corneal thickness occurred in the treated superotemporal, untreated central, and untreated superonasal quadrants after argon laser iridotomy.¹⁰ In the present study, we showed a small decrease in corneal endothelial cell count in the treated quadrant after Nd:YAG laser iridotomy ($P = .04$). Although possibly of minimal clinical

significance, these findings suggest that definable short-term damage does occur to the corneal endothelium overlying the Nd:YAG iridotomy site. Attention should be given to the long-term status of the corneal endothelium after Nd:YAG laser iridotomy.

References

1. Drake, M. V.: Neodymium:YAG laser iridotomy. *Surv. Ophthalmol.* 32:171, 1987.
2. Schwartz, L. W., Moster, M. R., Spaeth, G. L., Wilson, R. P., and Poryzees, E.: Neodymium-YAG laser iridectomies in glaucoma associated with closed or occludable angles. *Am. J. Ophthalmol.* 102:41, 1986.
3. Robin, A. L., and Pollack, I. P.: A comparison of neodymium:YAG and argon laser iridotomies. *Ophthalmology* 91:1011, 1984.
4. ———: Q-switched neodymium-YAG laser iridotomy in patients in whom the argon laser fails. *Arch. Ophthalmol.* 104:531, 1986.
5. Kerr Muir, M. G., and Sherrard, E. S.: Damage to the corneal endothelium during Nd:YAG photodisruption. *Br. J. Ophthalmol.* 69:77, 1985.
6. Snedecor, G. W., and Cochran, W. G.: *Statistical Methods*, ed. 7. Ames, Iowa, Iowa State University Press, 1980, pp. 102–105.
7. Berger, C. M., Lee, D. A., and Christensen, R. E.: Anterior lens capsule perforation and zonular rupture after Nd:YAG laser iridotomy. *Am. J. Ophthalmol.* 107:674, 1989.
8. Meyer, K. T., Pettit, T. A., and Straatsma, B. R.: Corneal endothelial damage with neodymium YAG laser. *Ophthalmology* 91:1022, 1984.
9. Dragon, D. M., Robin, A. L., Pollack, I. P., Quigley, H. A., Green, W. R., Murray, T. G., Hotchkiss, M. L., and D'Anna, S.: Neodymium:YAG laser iridotomy in the cynomolgus monkey. *Invest. Ophthalmol. Vis. Sci.* 26:789, 1985.
10. Panek, W. C., Lee, D. A., and Christensen, R. E.: Effects of argon laser iridotomy on the corneal endothelium. *Am. J. Ophthalmol.* 105:395, 1988.

AMERICAN JOURNAL OF OPHTHALMOLOGY®

FRANK W. NEWELL, *Publisher and Editor-in-Chief*
Suite 1415, 435 North Michigan Ave., Chicago, Illinois 60611

EDITORIAL BOARD

Thomas M. Aaberg, *Atlanta*

Jules Baum, *Boston*

William M. Bourne, *Rochester*

Ronald M. Burde, *New York*

Fred Ederer, *Bethesda*

Frederick T. Fraunfelder, *Portland*

Michael A. Kass, *St. Louis*

Steven G. Kramer, *San Francisco*

Irving H. Leopold, *Irvine*

Robert Machemer, *Durham*

Nancy M. Newman, *San Francisco*

Don H. Nicholson, *Miami*

Edward W. D. Norton, *Miami*

Deborah Pavan-Langston, *Boston*

Allen M. Putterman, *Chicago*

Dennis Robertson, *Rochester*

Merlyn M. Rodrigues, *Baltimore*

Stephen J. Ryan, *Los Angeles*

Jerry A. Shields, *Philadelphia*

M. Bruce Shields, *Durham*

Ronald E. Smith, *Los Angeles*

Bruce E. Spivey, *San Francisco*

Bradley R. Straatsma, *Los Angeles*

H. Stanley Thompson, *Iowa City*

E. Michael Van Buskirk, *Portland*

Gunter K. von Noorden, *Houston*

Published monthly by the OPHTHALMIC PUBLISHING COMPANY
Suite 1415, 435 North Michigan Avenue, Chicago, Illinois 60611

Directors

Edward W. D. Norton, *President*

Bradley R. Straatsma, *Vice President*

Frank W. Newell, *Secretary and Treasurer*

Bruce E. Spivey

Thomas M. Aaberg

Michael A. Kass

EDITORIALS

A Plea for Low Tech

Steven G. Kramer

While attending a recent corneal surgery symposium in honor of the late Max Fine, M.D., I found myself wondering what the master of the quintessential ocular operation would think of a corneal trephine that occupies the better part of a room and costs more than \$400,000. Max Fine's genius was his emphasis on meticulous, direct, and simple surgical techniques. He was proud, I think, of being able to do a complicated operation with few instruments designed for their simplicity. Consider, for example, the classic lines of the Max Fine forceps.

At the corneal symposium, we heard of excimer lasers for corneal trephination, for the correction of astigmatism, and for total corneal remodeling. Computerized topographic analysis systems were being coupled with other laser technologies to change the curvature of the cornea. Speakers envisioned an operation in which the surgeon would press one button on a console to analyze corneal topography and press a second button to reshape the cornea. I did not learn if the surgeon wore gown and gloves for the process. I did have the impression

that the surgery would cost many thousands of dollars per eye.

Notwithstanding the teaching of my mentors from more conservative times, I would not wish to be thought of as a therapeutic nihilist. Perhaps eliminating a lifelong dependency on spectacles or the slight but significant hazard of contact lenses is a worthwhile goal at any cost, and if such procedures were to become safe and commonplace, the cost of the instrumentation might even be reduced. What ophthalmologists have to consider, I suppose, is whether they wish their future patients to get their ophthalmic therapy from vending machines or in sun-tan parlors. It may not be too soon to begin mourning the death of ophthalmic surgery's art.

I also find myself pondering the coming changes in medical economics. Those of us in California can assure the rest of the nation that fee-for-service ophthalmic surgery as we have known it has passed on. We have already been caught in our own bind. Nationwide publicity convinced the general public and our governing

bodies that a cataract operation was a simple procedure that could be done in ten minutes. Why should we be surprised that there is resistance to paying a \$2,000 or \$3,000 fee for ten minutes of work? If our new technologic efforts are successful, one can surmise that a hefty reimbursement will be provided to pay the technical fee covering the cost of equipment while surgeons will be given a few dollars for knowing which buttons to push.

As we ophthalmologists become more like technicians aided by machines from the dizzyingly high-tech environment of Silicon Valley, I think we also become increasingly dehumanized. Are we to be physicians or mechanics? Do we train our residents in the human side of medicine, or do they learn by our example that our traditional fascination with gadgetry has become total involvement with integrated circuitry and spiraling costs? Is it at all possible that our increasingly high-tech future will still allow us to train skillful young physicians who think and who care?

In the symposium, there also seemed to be renewed interest in lamellar keratoplasty for various purposes, both tectonic and optical. Part of this interest, I found myself thinking, has occurred because an elaborate microkeratome (costing approximately \$15,000) was invented to cut a precise slice of cornea that could then be frozen and lathed for refractive procedures. As this technology has begun to die of its own weight, the microkeratome still survives because it can be used to cut a thin lamellar graft. What I found preposterous was the notion that the sharp mechanical blade was actually making its cut between corneal lamellae. Conversely, at the same symposium we saw a classic film of Max Fine preparing a lamellar

button by interlamellar dissection with a Gill knife, which he modified secretly for that purpose. Even without the modification, for years I have created lamellar buttons by blunt interlamellar dissection, which creates a corneal pocket and allows preparation of an excellent lamellar graft. I think the instrument I use costs approximately \$50.

As a corneal transplant surgeon considering the progress in my own field, my closing thoughts bring me back again to the corneal trephine. Will it ever be justified to use an excimer laser to create a 7.5-mm circular cut in the cornea? Perhaps not. But corneal surgeons today are not worth their salt if they do not use a modern suction trephine, which creates a precisely matched cut on both the donor and the recipient. In the excimer context, such a device sounds cheap at \$13,000 plus \$100 for a set of corneal blades used on each patient.

What is not at all clear is whether the \$13,000 investment makes a shred of difference. In the end, do not the multiple variables, including the depth and position of each suture bite, the recipient and donor preexisting corneal curvatures, and, most importantly, the variable biologic response of the patient, defeat our efforts to be absolutely precise about the angle of the trephine cut? Is there not an irreducible degree of unpredictability that cannot be significantly altered by the subtle difference between a skilled surgeon's use of one trephine or another? A certain amount of emphasis on low tech might not be a bad idea.

Reprint requests to Steven G. Kramer, M.D., Department of Ophthalmology, K301, University of California, San Francisco, CA 94143-0730.

Senile Accommodative Degeneration (SAD)

Arthur Jampolsky

The use of the pejorative and demeaning term of senile macular degeneration (SMD) still lingers on. Patients in their 50s and 60s with early age-related maculopathy (ARM) will welcome the analogous construct I suggest for the renaming of presbyopia, as senile accommodative degeneration (SAD); that is, renaming it for a sufficient period of time until ophthalmic practitioners and researchers develop a consistent awareness that senile macular degeneration has outlived its practical usefulness as a term, and that informed and sensitive professionals have agreed to use the scientifically more accurate and less demeaning term of age-related maculopathy, or simply, maculopathy.

SMD, senile macular degeneration; "senile" indeed, often occurs at 50 or 60 years of age in otherwise physically and mentally healthy individuals! "Age-related" does sound better than "senile." "Degeneration" indeed; only so much as the accommodative amplitude has also degenerated in otherwise physically and mentally healthy individuals in their 40s. "Maculopathy" does sound better than "degeneration."

For the sake of consistently inappropriate matching terminology, let us call presbyopia SAD, senile accommodative degeneration. It is SAD. SMD and SAD, why not?

A cataract is a cataract, at any age, from whatever cause. Glaucoma is glaucoma, at any age, from whatever cause. Maculopathy is maculopathy, at any age, from whatever cause. It may be early development, from retinotoxins, solar-induced, from retinal detachment, and the like. So why not just maculopathy, with the appropriate descriptors, just as we do for congenital cataract or for glaucoma?

Some well-meaning professionals, in attempting to change from senile macular degeneration to age-related maculopathy, get it only half right. Age-related macular degeneration is a term used in various publications and research papers.

Is it realistic to expect professionals to discard an ill-chosen term, such as senile macular degeneration (SMD), and to substitute another? It certainly happened with nuclear magnetic resonance (NMR), the term used when this imaging technique was first clinically introduced. It was easily changed to magnetic reso-

nance imaging (MRI), since nuclear did not sell well. The term SMD (senile macular degeneration) does not sell well to the thousands of so-labeled, otherwise healthy individuals in their 50s and 60s with some maculopathy.

Today, only a bold and venturesome surgeon would tell patients that they have a degenerated lens or a senile cataract. Neither one sells well. Most people (even surgeons) have a learning curve in a competitive environment. So wise surgeons use neither the senile nor the degeneration, and simply call it cataract.

Why not call the other simply maculopathy? Then everyone can have at it with the appropriate descriptor: hereditary, diabetic, traumatic, or age-related.

So until the S and the D are dropped for good from SMD, it appears only fair, and scientifically consistent, to propose the use of the term senile accommodative degeneration (SAD) for presbyopia.

Until age-related maculopathy, or simply maculopathy, comes into common usage consistent with other terminology, such as cataract or glaucoma, I would point out to all those otherwise healthy individuals in their 40s who need a visual aid, called a reading glass or a bifocal, to overcome a visual disability, they should feel comforted to know that they have a degenerated accommodative mechanism brought on by a senile process that begins in the teens. SAD, isn't it?

Editor's note—We at The Journal are often confused by abbreviations and acronyms and try to minimize their use as much as possible. The problem originates with the different meanings of the same letters. Our handy reference, "Medical Abbreviations," lists SAD as seasonal affective disorder, Self-Assessment Depression (Scale), subacute dialysis, and sugar and acetone determination. ARM does little better: anxiety reaction mild and artificial rupture of membranes. Thanks to Dr. Jampolsky's concern, it seems unlikely that an ophthalmologic SAD will join the list.

Reprint requests to Arthur Jampolsky, M.D., Smith-Kettlewell Eye Research Institute, 2232 Webster St., San Francisco, CA 94115.

LETTERS TO THE JOURNAL

Sector Palsy of the Sphincter Pupillae Muscle After Argon Laser Trabeculoplasty

Norbert Pfeiffer, M.D.,
and Guntram Kommerell, M.D.

Universitäts-Augenklinik Mainz (N.P.) and Freiburg (G.K.).

Inquiries to Norbert Pfeiffer, M.D., University Eye Hospital, Langenbeckstr. 1, D-6500 Mainz, Germany.

Argon laser trabeculoplasty generally is a safe procedure for the treatment of open-angle glaucoma. We encountered an unusual complication in a patient.

Primary open-angle glaucoma was diagnosed in the right eye of a 36-year-old man with intraocular pressure up to 30 mm Hg. The left eye was severely amblyopic because of myopia of -30 diopters. Primary argon laser trabeculoplasty was recommended for the right eye and performed as follows: pilocarpine and a local anesthetic were instilled into the conjunctival sac. One hundred laser burns were applied at the trabecular meshwork (spot-size, 50 μ m; duration, 0.1 millisecond; energy, approximately 1,000 mW to achieve whitening of the tissue). During the treatment no abnormality was noticed. One hour postoperatively intraocular pressure was normal. On the following day (after pilocarpine-induced miosis had worn off), the patient noticed that his right pupil was irregular and was wider than his left. He was sensitive to light and had blurred vision. Because he felt considerably handicapped in his only good eye and had not been warned about

anisocoria and blurred vision, he considered suing his ophthalmologist for malpractice. One month later, the patient came for a second opinion to our hospital.

On dark examination, both pupils were round and of equal size. With light and at near, the right pupil failed to constrict in the nasal sector between the 2 and 5 o'clock meridians. The rest of the pupil constricted normally (Figure). No abnormalities were disclosed on slit-lamp examination and gonioscopy. In the right eye visual acuity was 20/20 (-4.50 -1.75 \times 65) and accommodation was normal (8 diopters). In the left eye, the pupil was normal, and visual acuity was 2/60 (-30 diopters). After instillation of one drop of pilocarpine 0.1% into each eye, the pupil of the right eye constricted, whereas the pupil of the left eye was unchanged. The refraction of both eyes remained unchanged.

Dark sunglasses in bright light were recommended, and the patient was instructed to instill a drop of 0.1% pilocarpine in his right eye several times a day.

Fourteen months later, the patient reported that the right pupil had gradually become round. On examination, the right pupil constricted readily to light and near. A slight residual paresis was indicated by a flattening of the curvature in the nasal sector and a nasal displacement of the pupil by approximately 0.3 mm (Figure).

We believe the sector palsy of the sphincter pupillae muscle was caused by argon laser trabeculoplasty. The palsy was discovered on the day after treatment, and it had disappeared 15

THE JOURNAL welcomes letters that describe unusual clinical or pathologic findings, experimental results, and new instruments or techniques. The title and the names of all authors appear in the Table of Contents and are retrievable through the Index Medicus and other standard indexing services. Letters must not duplicate data previously published or submitted for publication. Each letter must be accompanied by a signed disclosure statement and copyright transfer agreement published in each issue of THE JOURNAL.

Letters must be typewritten, double-spaced, on 8 1/2 \times 11-inch bond paper with 1 1/2-inch margins on all four sides. (See Instructions to Authors.) An original and two copies of the typescript and figures must be sent. The letters should not exceed 500 words of text. A maximum of two black-and-white figures may be used; they should be cropped to a width of 3 inches (one column). Color figures cannot be used. References should be limited to five.

Letters may be referred to outside editorial referees for evaluation or may be reviewed by members of the Editorial Board. All letters are published promptly after acceptance. Authors do not receive galley proofs but if the editorial changes are extensive, the corrected typescript is submitted to them for approval.

These instructions markedly limit the opportunity for an extended discussion or review. Therefore, THE JOURNAL does not publish correspondence concerning previously published letters.

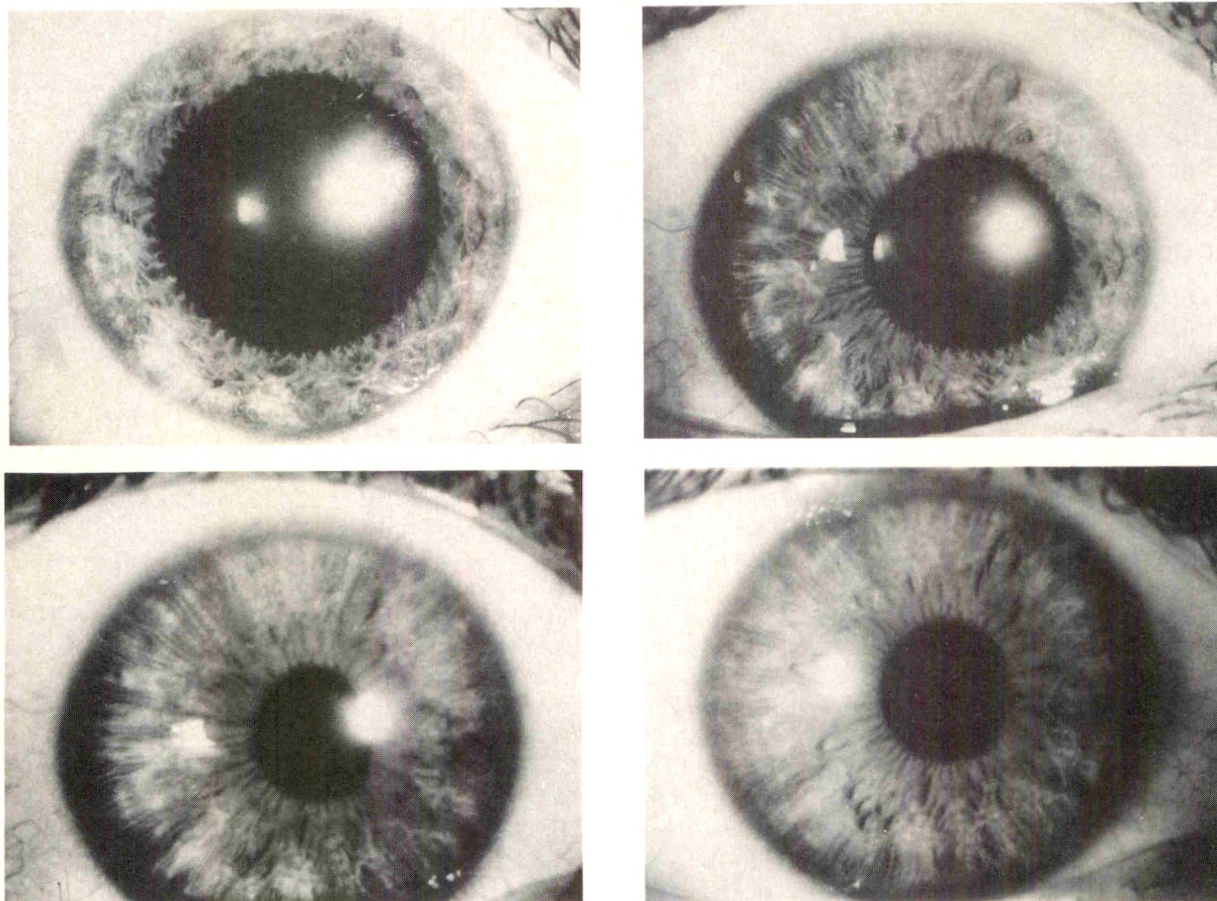


Figure (Pfeiffer and Kommerell). Right pupil one month after argon laser trabeculoplasty. Top left, in the dark; top right, contracted in the light; bottom left, after pilocarpine 0.1%; and bottom right, contracted in the light, 15 months after argon laser trabeculoplasty.

months later, which strongly suggests a causal relationship. The sector palsy was caused by a defect of innervation rather than a lesion of the muscle since denervation supersensitivity could be demonstrated. A tonic pupil is unlikely because the palsy was limited to one sector, accommodation was normal, and recovery was almost complete. We believe that parasympathetic fibers were hit by the argon laser trabeculoplasty near the chamber angle. The parasympathetic fibers enter the iris as large trunks, which break up into a plexus.¹ Thus, even a single laser burn hitting a trunk might produce a sector palsy. It is not necessary to postulate a laser burn at the base of the iris. Rather, it seems possible that some of the trunks loop forward (similar to Axenfeld's loops) before turning back to enter the iris. Such a loop might be hit near the trabecular meshwork during routine argon laser trabeculoplasty.

Sector palsies of the sphincter pupillae muscle are known to occur after photocoagulation of the peripheral retina.^{2,3} This complication seems to be rare but may only be masked by glaucoma medications that affect pupil size.

References

1. Duke-Elder, S., and Wybar, K. C.: The Anatomy of the Visual System. In Duke-Elder, S. (ed.): *System of Ophthalmology*, vol. 2. London, Henry Kimpton, 1961, pp. 167-185.
2. Rogell, G. D.: Internal ophthalmoplegia after argon laser panretinal photocoagulation. *Arch. Ophthalmol.* 97:904, 1979.
3. Lobes, L. A., and Bourgon, P.: Pupillary abnormalities induced by argon laser photocoagulation. *Ophthalmology* 92:234, 1985.

Nd:YAG Laser Treatment for Recurrent Hyphemas in Pseudophakia

Lawrence J. Geisse, M.D.

Department of Ophthalmology, St. Mary Medical Center.

Inquiries to Lawrence J. Geisse, M.D., 2572 Atlantic Ave., Long Beach, CA 90806.

Recurrent hyphemas after cataract surgery and placement of an intraocular lens have a variety of causes. Modern surgical techniques have made vascular ingrowth of the incision relatively uncommon.¹ Iris blood vessels subjected to repeated mechanical trauma by an intraocular lens are currently the most common source of the bleeding. With iris-plane lenses, the leaking iris vessels are usually at the pupillary margin.^{2,3} With posterior chamber and anterior chamber lenses, iris vessels can be affected at several different locations.^{3,4}

Identifying the exact location of the bleeding is often difficult, although the following may be helpful: iris angiography; examining the patient during an active hemorrhage; finding a clot on a vessel; and finding discrete areas of iris erosion by retroillumination.⁴

Treatment success can often be achieved by medical means (that is, mydriasis or miosis). If eyedrops fail, then argon laser treatment to the leaking site may be attempted. Repeated laser treatments are often necessary, however, which leave an irregular, dilated pupil and subject the patient to further bleeding. Occasionally, removal of the intraocular lens may be necessary.

I successfully used an Nd:YAG laser to treat two patients with posterior chamber intraocular lenses who had recurrent hyphemas for more than one year. Medical treatment was ineffective in both patients. Argon laser treatment directed by iris angiography was performed in one patient but had not stopped the bleeding. Hemorrhages occurred in both patients every four to five weeks and ranged from minor blurring of vision to macroscopic hyphemas of 30% of the total anterior chamber volume.

Upon examination, each patient was found to have a transillumination defect of the iris corresponding to contact of the iris with the optic of the intraocular lens. In both patients, an iris vessel could be seen traversing this area. It was thought that intermittent trauma to this vessel was responsible for the recurrent bleeding.

The vessel was followed peripherally until it

could be seen outside the transillumination defect (and the intraocular lens optic). An iridotomy was then created with an Nd:YAG laser to include the previously identified vessel outside (peripheral to) the edge of the transillumination defect (one to four pulses at 5 mJ delivered through an Abraham iridectomy contact lens). A small amount of bleeding occurred but stopped immediately with slight pressure.

Since this procedure, neither patient has had a hemorrhage in more than two years of follow-up. Atrophy of the iris vessel central to the iridotomy could be seen, which eliminated the possibility of rebleeding. No other changes in the iris or the eye were noted.

In cases of recurrent hyphemas after cataract extraction with placement of an intraocular lens in which a leaking iris vessel can be identified, Nd:YAG laser disruption of this vessel peripheral to the edge of the intraocular lens is simple, effective, and has the advantage of avoiding chronic pharmacologic treatment or laser-induced distortions of the pupil.

References

1. Swan, K. C.: Hyphema due to wound vascularization after cataract extraction. *Arch. Ophthalmol.* 89:87, 1973.
 2. Ellingson, F. T.: The uveitis-glaucoma-hyphema syndrome associated with the Mark VIII anterior chamber lens implant. *Am. Intraocular Implant Soc. J.* 4:50, 1978.
 3. Lieppman, M. E.: Intermittent visual "white-out." A new intraocular lens complication. *Ophthalmology* 89:109, 1982.
 4. Johnson, S. H., Kratz, R. P., and Olson, P. F.: Iris transillumination defect and microhyphema syndrome. *Am. Intraocular Implant Soc. J.* 10:425, 1984.
-

Chronic Ciliary Pain Secondary to Posterior Chamber Intraocular Lens Loop Incarceration

Ulrich F. C. Legler, M.D.,
David J. Apple, M.D.,
Paul Hund, M.D.,
and Waite S. Kirkconnell, M.D.

Departments of Ophthalmology (U.F.C.L., D.J.A., P.H.) and Pathology (D.J.A.), Center for Intraocular Lens Research, Storm Eye Institute, Medical University of South Carolina. Dr. Kirkconnell is in private practice in Tampa, Florida.

Inquiries to David J. Apple, M.D., Department of Ophthalmology, Medical University of South Carolina, 171 Ashley Ave., Charleston, SC 29425.

Pain associated with anterior chamber intraocular lenses has long been a recognized complication,¹ especially with rigid or improperly sized lenses. We treated a patient with a complication of ciliary fixation, namely chronic pain apparently induced by mechanical pressure and irritation on the iris root-ciliary body by a posterior chamber intraocular lens loop.

A 73-year-old woman with a history of bilateral blepharoplasty underwent a routine extracapsular cataract extraction with implantation of a posterior chamber intraocular lens in the right eye on Oct. 23, 1986. According to the operative note, capsular fixation was attempted; there was no mention of dialing the intraocular lens, and the lens was positioned vertically. Postoperatively, she had pain and a foreign body sensation under her right eyelid. Examination disclosed visual acuity of 20/100 and mild conjunctival injection, and slit-lamp examination showed rare cells and flare. The posterior chamber intraocular lens was stated to be in excellent position. Results of fundus examination and intraocular pressure were within normal limits. Initially, her symptoms were believed to be an allergic reaction to antibiotic eyedrops that had been administered postoperatively. This medication was discontinued, and corticosteroids were used. The foreign body sensation, however, progressed to a point where she had severe pain, tearing, and burning. She was referred to numerous eye centers and a wide variety of diagnoses were made, including allergic reaction, irritation from the sutures, dry eyes, lagophthalmos, and eyelid laxity. Treatments included lubricants, corticosteroids, eye patches, and removal of one exposed suture in the corneal incision, but none of these provided relief of pain and tearing. She also underwent bilateral lateral canthoplasty and tightening of the lower eyelid. No consultant suspected the intraocular lens as a factor in the pathogenesis of her problem. The patient continued to have pain in the eye.

The first documentation regarding the fixation of the intraocular lens occurred four years postoperatively in March 1990. The intraocular lens was noted to be malpositioned superiorly, with the superior loop eroding through the iris and causing pigment loss. The inferior loop was within the capsule. Suspecting that chronic iris chafing and pressure of the superior uveal-fixated loop may have caused the patient's

symptoms, surgical repositioning was performed. The intraocular lens was rotated so that the superior loop was moved from the site of the iris contact into the ciliary sulcus in a horizontal position. The inferior loop was also noted to have adhesions with retained cortical material. This loop was disengaged with some difficulty and rotated in the ciliary sulcus. The pain subsided almost immediately after lens rotation. Ten months postoperatively, the patient has had no further pain, and visual acuity has improved from 20/100 to 20/30.

The patient had chronic pain that was caused by loop incarceration of an asymmetrically fixated (capsule-sulcus) posterior chamber intraocular lens. The uveal-fixated loop had eroded into the iris root, which caused episodic chronic uveitis. Erosion of loops into ciliary body tissue and irritation of the posterior iris surface by intraocular lens loops have been previously described as the posterior iris chafing syndrome.^{1,2} Uveal-fixated loops are always situated in or near a rich vascular plexus and a stroma containing highly metabolic cells.³ Mechanical damage to uveal tissue is likely to provoke a breakdown of the blood-aqueous barrier with release of blood or tissue products (for example, inflammatory mediators such as prostaglandins or oxidative-free radicals), which causes acute or chronic inflammation.^{3,4}

In most instances, the formation of a fibrous membrane around the loops or haptics at the site of contact with uveal tissue prevents a persistent breakdown of the blood-aqueous barrier and the onset of chronic inflammation. Occasionally, the continuous movement of the iris and ciliary body against a protruding haptic may inhibit formation of the protective fibrous membrane. The severity or intensity of the breakdown of the blood-aqueous barrier partially determines what clinical signs a patient may have. These signs range from subclinical or symptomatic inflammation to severe uveitis with glaucoma and hyphema.² The results of a study by Miyake, Asakura, and Kobayshi,⁵ in which the effect of different types of intraocular lens fixation on the blood-aqueous barrier were analyzed by fluorophotometry, showed that the least barrier disruption was in eyes with posterior chamber intraocular lenses with intracapsular fixation. The findings in this case suggest the biologic merit of capsular fixation. The complete isolation of the intraocular lens within the avascular posterior capsule, away from the metabolically active ciliary body and iris, apparently explains these results.

The differential diagnosis for the ocular pain in our patient was complicated by her dry eyes and history of eyelid surgery. Not until the iris erosion was discovered and the superior loop noted to be in contact with the iris was the underlying cause for the chronic pain elucidated. In this case, the pathophysiologic characteristics involved the asymmetric loop fixation (capsule-sulcus) with erosion of the upper loop into uveal tissue. The problem was probably exacerbated by contraction and cicatrization of the capsular-fixed inferior loop that augmented the pressure and erosion of the opposite superior loop. When the loops were repositioned horizontally into symmetric fixation (sulcus-sulcus) to prevent continuous chafing by the loops against the iris, the patient's symptoms resolved.

References

1. Apple, D. J., Mamalis, N., Loftfield, K., Googe, J. M., Novak, L. C., Kavka-Van Norman, D., Brady, S. E., and Olson, R. J.: Complications of intraocular lenses. A historical and histopathological review. *Surv. Ophthalmol.* 29:1, 1984.
2. Apple, D. J., Mamalis, N., Reidy, J. J., Novak, L. C., Googe, J. M., Loftfield, K., and Olson, R. J.: A comparison of ciliary sulcus and capsular bag fixation of posterior chamber lenses. *Am. Intraocular Implant Soc. J.* 11:44, 1985.
3. Morrison, J. C., and Van Buskirk, E. M.: Anterior collateral circulation in the primate eye. *Ophthalmology* 90:707, 1983.
4. Apple, D. J., Mamalis, N., Olson, R. J., and Kincaid, M. C.: *Intraocular Lenses. Evolution, Designs, Complications and Pathology.* Baltimore, Williams & Wilkins, 1989, pp. 226-229.
5. Miyake, K., Asakura, M., and Kobayashi, H.: Effect of intraocular lens fixation on the blood-aqueous barrier. *Am. J. Ophthalmol.* 98:451, 1984.

Recurrent Uveitis Preceded by Swelling of Skin Tattoos

Ahmad M. Mansour, M.D.,
and Chi-Chao Chan, M.D.

Laboratory of Immunology, National Eye Institute, National Institutes of Health (C.-C.C.), and Department of Ophthalmology, University of Texas Medical Branch (A.M.M.).

Inquiries to Chi-Chao Chan, M.D., National Eye Institute, Bldg. 10, Room 6C416, 9000 Rockville Pike, Bethesda, MD 20892.

A 35-year-old man was treated from 1982 to 1989 because of uveitis. Extensive skin tattoos had been applied to the forearms in 1960 and to the chest and back in 1970 (Fig. 1). Since 1977, the patient developed recurrent simultaneous swelling of the various tattoo sites on his forearms and back; and since 1982, this swelling repeatedly preceded the ocular inflammation by one week. The ocular examination was characterized by recurrent episodes of moderate anterior nongranulomatous uveitis, initially in the left eye and involving the right eye a few days later. The cycle would last four weeks with one week of acute, red photophobic eyes followed by slight residual photophobia over the following three weeks. Three biopsy specimens from involved tattoo sites taken several years apart showed nonnecrotizing granulomas surrounding pigment granules (Fig. 2). Results of extensive laboratory, radiographic, and histopathologic studies (lung biopsy) were repeatedly negative. Immunopathologic examination of skin tattoos during the acute swelling phase showed the nests of infiltrating cells in the dermis to be composed mainly of T and B lymphocytes and macrophages with a ratio of 1.5:1:1. Most T lymphocytes bore IL-2 receptors, and T-helper to T-suppressor cell ratio was 1:1. Of the infiltrating cells, 90% stained positively for major histocompatibility complex class II antigens.

Most skin tattoos contain metallic compounds that are potentially sensitizing.¹ Metals found in tattoos include mercury, copper, iron,

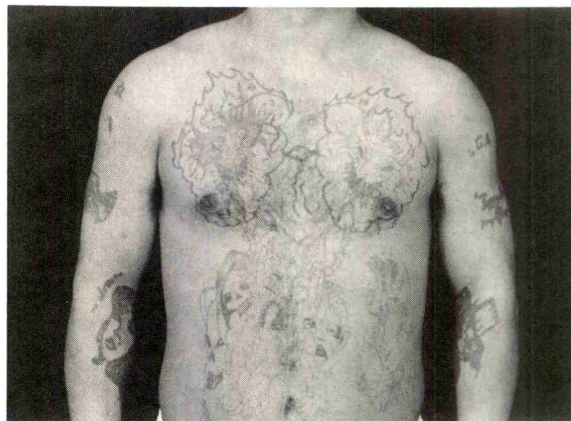


Fig. 1 (Mansour and Chan). Tattoos covering the chest and upper extremities.

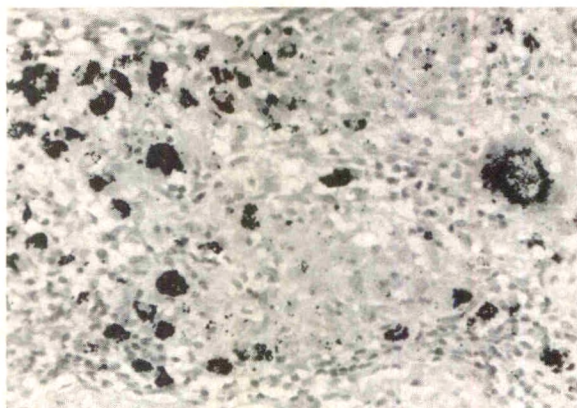


Fig. 2 (Mansour and Chan). Granuloma around black tattoo pigments (hematoxylin and eosin, $\times 100$).

and titanium. The histologic pattern of reaction to tattoos includes diffuse lymphohistiocytic infiltrate, lichenoid reaction, and sarcoidal granuloma.² Hanada, Chiyoya, and Katabira³ described the findings in a 31-year-old man who developed symptoms similar to those of systemic sarcoidosis after extensive tattooing. These included uveitis and noncaseating granulomatous reaction in skin tattoos, lymph nodes, and lung tissue.

This case demonstrated granuloma formation with predominance of mononuclear cells. The high ratio of B lymphocytes and macrophages and equal number of T-helper and T-suppressor cells are indicative of delayed hypersensitivity reaction, unlike that of sarcoidosis.^{4,5} The concurrent uveitis and skin induration at the site of tattoos appear related to the sensitizing character of tattoo material.

References

1. Slater, D. N., and Durrant, T. E.: Tattoos. Light and electron microscopy studies with x-ray microanalysis. *Clin. Exp. Dermatol.* 9:167, 1984.
2. Blumenthal, G., Okun, M. R., and Ponitch, J. A.: Pseudolymphomatous reaction to tattoos. Report of three cases. *J. Am. Acad. Dermatol.* 6:485, 1982.
3. Hanada, K., Chiyoya, S., and Katabira, Y.: Systemic sarcoidal reaction in tattoo. *Clin. Exp. Dermatol.* 10:479, 1985.
4. Chan, C.-C., Wetzig, R. P., Palestine, A. G., Kuwabara, T., and Nussenblatt, R. B.: Immunohistopathology of ocular sarcoidosis. Report of a case and discussion of immunopathogenesis. *Arch. Ophthalmol.* 105:1398, 1987.
5. Buechner, S. A., Winkelman, R. K., and Banks, P. M.: T-cell subsets in cutaneous sarcoidosis. *Arch. Dermatol.* 119:728, 1983.

Vertebral Artery Occlusion Complicating Perimetry

Jacques De Keyser, M.D.,
Luc Herroelen, M.D.,
and Luc Van Langenhove, M.D.

Departments of Neurology (J.D.K., L.H.) and Ophthalmology (L.V.L.), Academisch Ziekenhuis Vrije Universiteit Brussel.

Inquiries to Jacques De Keyser, M.D., Department of Neurology, Academisch Ziekenhuis Vrije Universiteit Brussel, Laarbeeklaan 101, B 1090 Brussels, Belgium.

A 65-year-old man had polycythemia vera, which was controlled by phlebotomies. He underwent automated perimetry because he saw black spots. Because the perimetrist did not adjust the height of the chin rest, the examination was carried out with the head of the patient hyperextended as shown in the Figure. Near the end of the test, which had lasted approximately 30 minutes, he noticed a vague pain in the high, lateral, right region of his neck. Five minutes later the patient suddenly had vertigo, nausea, dysarthria, visual distortion, and an unsteadiness of gait with a tendency to deviate to the right.

All symptoms gradually resolved over the next three days. One week later, neurologic examination showed no abnormalities. Blood pressure was 140/80 mm Hg and pulse was 80 beats per minute. Cardiac auscultation was normal. There were no vascular bruits. Computed tomography of the head was normal. Intravenous digital subtraction angiography disclosed occlusion of the right vertebral artery at the C1-C2 vertebral level. X-rays of the neck showed nothing unusual. The hematocrit level was 54.5%; the white blood cell count was $13.9 \times 10^3/\text{mm}^3$ with 83% neutrophils; the platelet count was $494 \times 10^3/\text{mm}^3$.

The patient had polycythemia vera, which is associated with an increased risk for cerebrovascular thrombosis. However, since hematocrit and platelet levels were only moderately increased, the patient's polycythemia vera could not be considered the cause of the cerebrovascular accident. The temporal relationship to the perimetric examination and the site

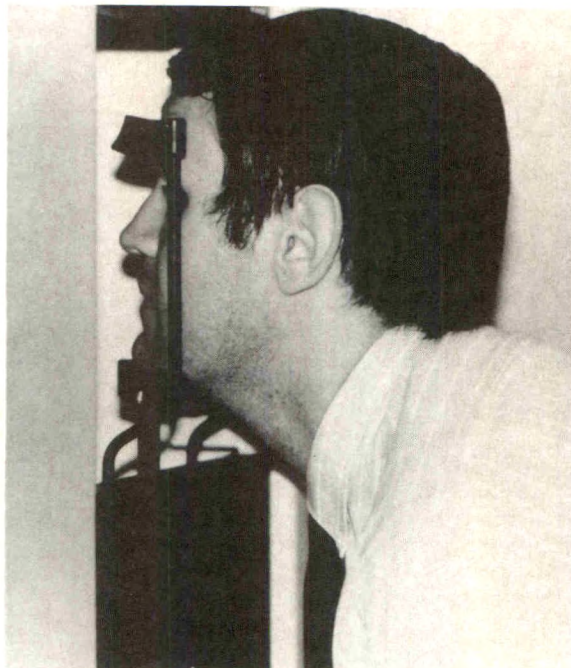


Figure (De Keyser, Herroelen, and Van Langenhove). Perimetry carried out with the head in hyperextension.

of the lesion leave little doubt that the vertebral artery occlusion was primarily caused by mechanical injury or compression of the vertebral artery across the craniovertebral junction, caused by cervical hyperextension. Similar cases of vertebral artery injury have been described after yoga,¹ gymnastic exercises,² overhead work,³ and neck manipulation.⁴

Clinic personnel should be instructed about the potential hazards of cervical hyperextension during diagnostic procedures.

References

1. Hanus, S. H., Homer, T. D., and Harter, D. H.: Vertebral artery occlusion complicating yoga exercise. *Arch. Neurol.* 34:574, 1977.
2. Nagler, W.: Vertebral artery obstruction by hyperextension of the neck. Report of three cases. *Arch. Phys. Med. Rehabil.* 54:237, 1973.
3. Okawara, S., and Nibbelinck, D.: Vertebral artery occlusion following hyperextension and rotation of the neck. *Stroke* 5:640, 1974.
4. Mehlic, T., and Farhat, S. M.: Vertebral artery injury from chiropractic manipulation of the neck. *Surg. Neurol.* 2:125, 1974.

Terrien's Marginal Degeneration Associated With Vernal Conjunctivitis

Israel Kremer, M.D.

Department of Ophthalmology, Beilinson Medical Center, Petah Tiqva, Sackler School of Medicine, Tel Aviv University.

Inquiries to Israel Kremer, M.D., Department of Ophthalmology, Beilinson Medical Center, Petah Tiqva 49100, Israel.

Terrien's disease of the peripheral cornea is characterized by a slowly progressive, noninflammatory, marginal corneal furrowing and ectasia of the superior peripheral cornea.¹ Suveges, Levai, and Albert¹ noted phagocytosis of corneal stroma by cells resembling histiocytes associated with peripheral corneal blood vessels in the ectatic areas. The origin of Terrien's disease is still unknown, but the presence of lipid associated with the furrowing suggests a degenerative process.

Patients with Terrien's disease are usually asymptomatic, unless they have severe irregular astigmatism. Most patients do not have significant associated ocular inflammation. Austin and Brown,² however, described six patients with a combination of severe recurrent episodes of painful ocular inflammation and corneal findings typical of Terrien's disease. Binder, Zavala, and Stainer³ similarly described a patient who had both the corneal changes of Terrien's degeneration and moderately severe ocular inflammation. I treated a patient who had chronic limbal vernal conjunctivitis and developed Terrien's degeneration.

A 40-year-old man had severe vernal conjunctivitis, both palpebral and limbal, during childhood. He was treated with corticosteroid and disodium-cromoglycate eyedrops for almost ten years, and at the age of 17 years, he was free of symptoms. Subsequently, he began having visual disturbances. Refraction disclosed 4 diopters of against the rule astigmatism in addition to -4.0 spheres in both eyes. Slit-lamp examination disclosed peripheral superior corneal opacification with mild, superficial vascularization. Corneal thinning was also noted in that area. The corneal findings progressed during the following years, and the superior stromal thinning continued gradually, extending peripherally and centrally (Figure), which led to ectasia, increased against the rule astigmatism, and diminution of visual acuity.

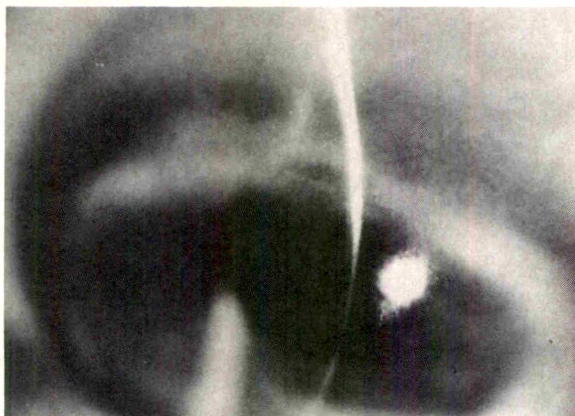


Figure (Kremer). Slit-lamp photograph of a superior band of corneal opacification and some vascularization, in addition to localized thinning with superior corneal ectasia.

Keratometry disclosed R.E.: 52 diopters horizontal and 44 diopters vertical and L.E.: 51 diopters horizontal and 43 diopters vertical. In both eyes, a typical progression of Terrien's degeneration was found, which consisted of superior peripheral corneal opacification, mild vascularization, thinning, and ectasia. The patient was intolerant to contact lenses, because he developed giant papillary conjunctivitis, and therefore had to wear spectacles. Best-corrected visual acuity was 20/40 bilaterally.

Unlike the association of keratoconus with vernal conjunctivitis,⁴ other types of noninflammatory corneal ectasia, such as superior corneal thinning and pellucid marginal degeneration, have been reported to be associated with vernal conjunctivitis. Cameron, Al-Rajhi, and Badr⁵ studied 61 patients with different corneal ectasia and vernal keratoconjunctivitis. Fifty-three patients had keratoconus, five had pellucid marginal degeneration, two had keratoglobus, and only one patient had superior corneal thinning. In vernal keratoconjunctivitis, eye rubbing is common because of the intense itching; several authors have commented on the role of chronic eye rubbing in keratoconus. The variety of corneal thinning patterns in association with vernal keratoconjunctivitis found in this report⁵ supports eye rubbing as one of the major factors in the cause of corneal ectasia. In my opinion, the active limbal vernal keratitis per se, with the eosinophilic infiltration reaching the peripheral cornea, may be another important pathogenetic factor in my patient. Limbal vernal keratoconjunctivitis was

also found in the patient described by Cameron, Al-Rajhi, Badr.⁵

References

1. Suveges, I., Levai, G., and Albert, B.: Pathology of Terrien's disease. Histochemical and electron microscopic study. *Am. J. Ophthalmol.* 74:1191, 1972.
2. Austin, P., and Brown, S. I.: Inflammatory Terrien's marginal corneal disease. *Am. J. Ophthalmol.* 92:189, 1981.
3. Binder, P. S., Zavala, E. Y., and Stainer, G. A.: Noninfectious peripheral corneal ulceration. Morren's ulcer or Terrien's marginal degeneration? *Ann. Ophthalmol.* 14:425, 1982.
4. Khan, M. D., Kundi, N., Saeed, N., Gulab, A., and Nazeer, A. F.: Incidence of keratoconus in spring catarrh. *Br. J. Ophthalmol.* 72:41, 1988.
5. Cameron, J. A., Al-Rajhi, A. A., and Badr, I. A.: Corneal ectasia in vernal keratoconjunctivitis. *Ophthalmology* 96:1615, 1989.

Identification of Amiodarone in Corneal Deposits

Stephen J. Haug, M.D.,
and Alan H. Friedman, M.D.

Department of Ophthalmology, Mount Sinai Medical Center. This study was supported in part by an unrestricted grant from Research to Prevent Blindness, Inc.

Inquiries to Alan H. Friedman, Box 1183, Mount Sinai Medical Center, One Gustave L. Levy Place, New York, NY 10029-6574.

Amiodarone hydrochloride is an effective drug for the treatment of angina and ventricular arrhythmias. Its use has been associated with deposits in various tissues, including skin, nerves, and cornea.¹⁻³ Amiodarone has been identified in dermal macrophages by energy-dispersive x-ray microanalysis.³ We used this technique on amiodarone-related corneal deposits.

A 74-year-old man was given 400 mg of amiodarone per day after cardioversion for refractory ventricular tachycardia. Seven months later ophthalmologic consultation was obtained after hospital admission because of the amiodarone dosage. The interior portion of each cornea contained golden-brown deposits

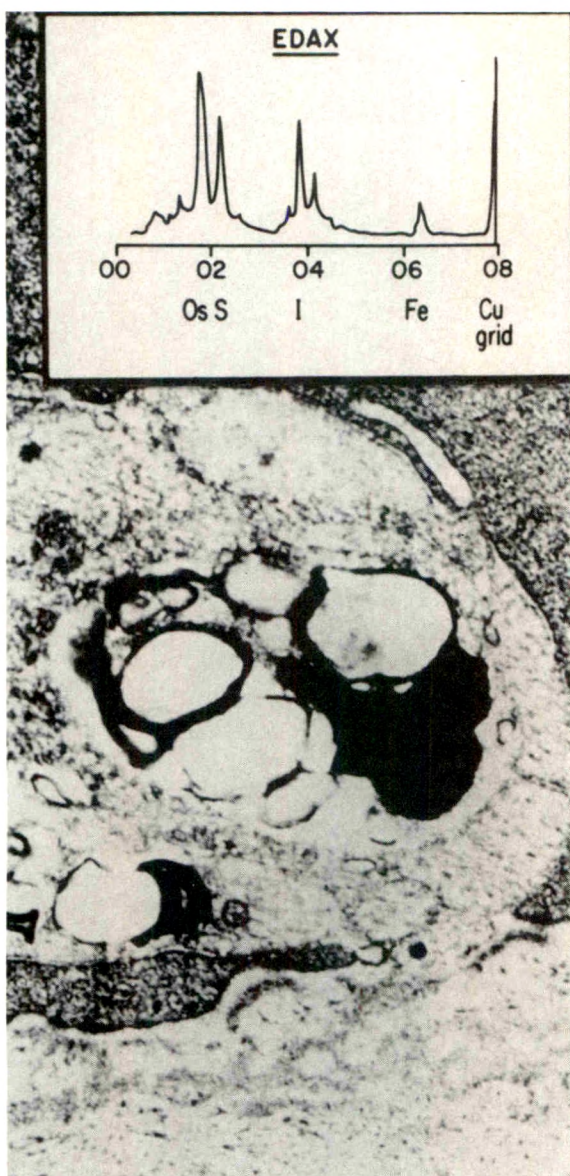


Figure (Haug and Friedman). Electron micrograph of corneal epithelium showing electron-dense lamellar inclusion bodies. Inset, Energy-dispersive x-ray microanalysis (EDAX) of inclusions showing high iodine content.

arranged in a linear whorl-shaped pattern. There was a clear zone between the terminus of the deposits and the corneoscleral limbus. We believed that the corneal deposits were typical of amiodarone.

Shortly after the examination, the patient underwent surgery for the treatment of his ventricular tachycardia. He died ten days later.

Postmortem histopathologic examination of

corneal tissue showed no evidence of deposits by light microscopy. The basal layer of epithelium, however, stained with Perl's stain. Transmission electron microscopy demonstrated electron-dense inclusions within basal epithelial cells of the cornea (Figure). These inclusions had a lamellar, fingerprint-shaped appearance. Energy-dispersive x-ray microanalysis of corneal basal epithelial cells showed a heavy concentration of iodine within the electron-dense inclusions (Figure, inset).

Corneal microdeposits have been reported to occur in more than 90% of patients taking amiodarone.^{1,4} Amiodarone and its major metabolite, desethylamiodarone, can be localized to the dermis of sun-exposed skin.³ Histopathologic studies of light-exposed skin disclosed middermal yellow-brown granular pigment, perivascular in distribution, localized within the cytoplasm of macrophages. On transmission electron microscopy, this pigment showed the same lamellar arrangement as was seen in the corneal epithelium of our patient. The high concentration of iodine in these inclusions presumably derives from amiodarone, which is rich in iodine.

Fabry's disease, chloroquine, chlorpromazine, hydroxychloroquine, suramin, and other drugs have been associated with both cornea verticillata and lamellar inclusion bodies.⁵ Drug-lipid complexes may resist enzymatic degradation leading to their accumulation in inclusions. Lipid deposits have been demonstrated in the lens epithelium, conjunctival fibrocytes, and conjunctival vascular endothelium of patients taking amiodarone.⁴

References

1. Orlando, R. G., Dangel, M. E., and School, S. F.: Clinical experience and grading of amiodarone keratopathy. *Ophthalmology* 91:1184, 1984.
2. Pellissier, J., Pouget, J., Cros, D., De Victor, B., Serratrice, G., and Toga, M.: Peripheral neuropathy induced by amiodarone chlorhydrate. A clinical study. *J. Neurol. Sci.* 63:251, 1984.
3. Zachary, C. B., Slater, D. N., Holt, D. W., Storey, G. C. A., and MacDonald, D. M.: The pathogenesis of amiodarone-induced pigmentation and phototoxicity. *Br. J. Dermatol.* 110:451, 1984.
4. D'Amico, D. J., Kenyon, K. R., and Ruskin, J. N.: Amiodarone keratopathy. Drug-induced lipid storage disease. *Arch. Ophthalmol.* 99:257, 1981.

5. Fraunfelder, F. T.: Drug-Induced Ocular Side Effects and Drug Interactions. Philadelphia, Lea and Febiger, 1989, pp. 60, 67, and 254.

Nosocomial Conjunctival Ophthalmomyiasis With *Cochliomyia macellaria*

James Chodosh, M.D.,
Jill E. Clarridge, Ph.D.,
and Alice Matoba, M.D.

Departments of Ophthalmology (J.C., A.M.) and Pathology (J.E.C.), Baylor College of Medicine, and Houston Veterans Affairs Medical Center (J.E.C., A.M.). This study was presented in part at the 27th annual meeting of the Baylor Ophthalmology Alumni Association, Houston, Texas, June 8, 1990.

Inquiries to James Chodosh, M.D., Cullen Eye Institute, Baylor College of Medicine, One Baylor Plaza, Houston, TX 77030.

Myiasis is a rare condition in which maggots, the larvae of flies, invade and feed on the living or dead tissues of humans or animals. Ophthalmomyiasis is maggot infestation of the eye or periocular tissues.

A 62-year-old man with a history of dementia and peripheral vascular disease was brought to the Houston Veterans Affairs Medical Center from a local nursing home because of fever. The ophthalmology service was consulted because of erythema and edema in each eye.

On examination, best-corrected visual acuity was 20/40 in each eye. The eyelids were edematous. A bloody, mucous discharge was present bilaterally. The conjunctiva were injected, chemotic, and ulcerated. At each medial canthus, several mobile larvae were seen (Fig. 1). The larvae appeared to avoid bright light, burrowing into the chemotic conjunctiva, but were successfully removed. The remainder of the ocular examination was unremarkable. The nose was free of larvae. The patient had a decubitus ulcer of the left foot in which no larvae were seen. He was admitted to the hospital and treated with intravenous antibiotics. No further larvae were found on subsequent examinations.

The larvae (Fig. 2) were identified as *Cochliomyia macellaria*. *Streptococcus* species, group G, grew in cultures of blood, conjunctiva, the foot ulcer, and from the larvae themselves, which

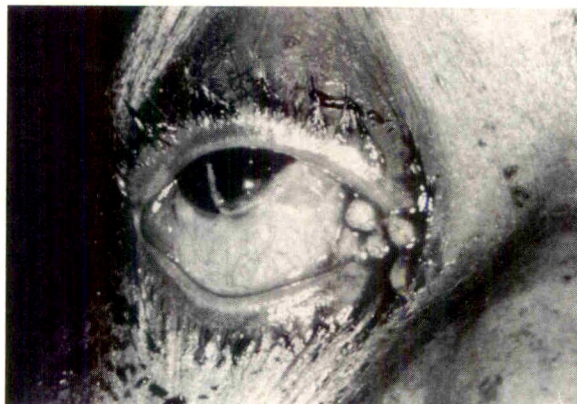


Fig. 1 (Chodosh, Clarridge, and Matoba). Right eye with several larvae at medial canthus.

were cultured by allowing them to crawl over a blood agar plate.

Management of external ophthalmomyiasis consists of mechanical removal of the maggots and a careful search for intraocular or cephalic involvement. Although not helpful in our case, one should consider culturing the larvae if the patient appears systemically ill, because maggots are vectors of bacterial disease. Repeated examination is recommended, since a few larvae are often missed on the first examination.

Maggot infestations are usually self-limited because larvae, when fully mature, generally leave their host to bury themselves in the soil. If allowed to invade deep into the orbit in large numbers, however, they may hatch into flies while still in the socket, producing the fly-blown orbit. This may result in death.¹

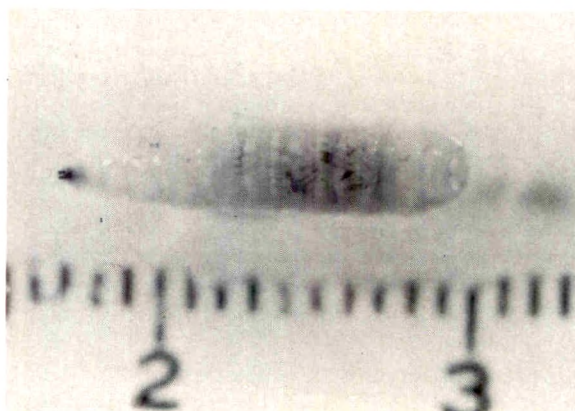


Fig. 2 (Chodosh, Clarridge, and Matoba). *Cochliomyia macellaria* after removal.

Nosocomial myiasis in the continental United States is rare. Hospital-acquired nasal myiasis with *C. macellaria* occurred in a comatose diabetic man.² One case of myiasis acquired in a convalescent home has been reported, which involved the skin donor graft site of a quadriplegic man.³

Patients at risk for nosocomial myiasis are those who are unable to fend off the advances of female flies in search of decomposing tissue, blood, or an open wound.⁴ The presence of flies within a health care facility should not be tolerated.

References

1. Duke-Elder, S., and MacFaul, P. A.: The Ocular Adnexa. Lacrimal, Orbital and Para-Orbital Diseases. In Duke-Elder, S. (ed.): System of Ophthalmology, vol. 13, pt. 2. St. Louis, C. V. Mosby, 1974, pp. 931-932.
2. Smith, D. R., and Clevenger, R. R.: Nosocomial nasal myiasis. Arch. Pathol. Lab. Med. 110:439, 1986.
3. Magnarelli, L. A., and Andreadis, T. G.: Human cases of furuncular, traumatic, and nasal myiasis in Connecticut. Am. J. Trop. Med. Hyg. 30:894, 1981.
4. Greenberg, B.: Two cases of human myiasis caused by *Phaenicia sericata* (Diptera: Calliphoridae) in Chicago area hospitals. J. Med. Entomol. 21:615, 1984.

Eyelid Tumors in the Proteus Syndrome

Alan Lessner, M.D.,
and Curtis E. Margo, M.D.

Departments of Ophthalmology (A.L., C.E.M.) and Pathology (C.E.M.), University of Florida, College of Medicine.

Inquiries to Alan Lessner, M.D., University of Florida, Box J-284, JHMHC, Gainesville, FL 32610.

The proteus syndrome is named after the sea-god Proteus, who could assume various shapes. It is an unusual disorder characterized by overgrowth of various body parts.^{1,2} Although the phenotypic expression of the disease is broad, most patients demonstrate skeletal malformations, multiple soft tissue tumors (particularly lipomas), cutaneous hamartomas, and visceral anomalies.³

A 42-year-old man was referred for treatment of several large tumors of his left upper eyelid. The lesions had been slowly enlarging for years. The patient was thoroughly examined at the department of medical genetics of our institution, and the systemic overgrowth disorder was diagnosed as the proteus syndrome. Since adolescence, the patient had numerous cutaneous and subcutaneous tumors excised from his trunk and face. Previous pathologic diagnoses included lipoma, angioliipoma, organoid nevus, and trichoepithelioma. Several individual lipomas removed from the flank and abdomen weighed more than 10 kg.

On examination, the patient had blepharoptosis secondary to several multilobulated tumors of the left eyebrow and upper eyelid (Fig. 1). The lesions were flesh colored and soft. Their surface contained dilated pores from which material resembling cheese could be expressed. Similar cutaneous nodules were present on the side of the nose, external nares, the side of the face, back, and abdomen. Best-corrected visual acuity was 20/20 in each eye, and results of the remainder of the ocular examination were normal. Leish nodes were not present. General examination disclosed massive subcutaneous lipomas in the neck, flank, and back. The patient had several malformed ribs and cranial exostoses. Neither café-au-lait maculae nor axillary freckling were present.

The eyebrow and eyelid masses were excised. Histologically the epidermis displayed mild acanthosis. Numerous small and large hair struc-

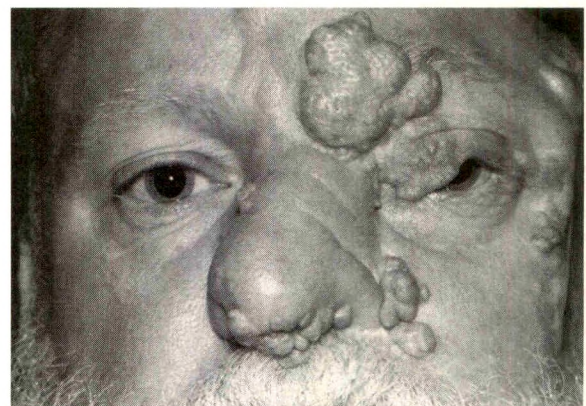


Fig. 1 (Lessner and Margo). Numerous multilobulated tumors are present on the left eyebrow, left upper eyelid, nose, and side of face. The overlying skin contains dilated pores.

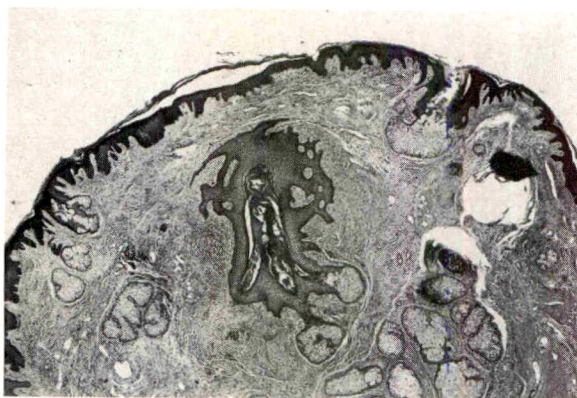


Fig. 2 (Lessner and Margo). An excised nodule displays small and large hair structures with mature sebaceous glands that open directly into dilated follicular infundibula. The hair structures are lined by hyperplastic squamous epithelium (hematoxylin and eosin, $\times 40$).

tures were associated with mature sebaceous glands (Fig. 2). Sebaceous glands often opened into dilated follicular infundibula lined by hyperplastic epithelium and filled with keratin debris. Infundibula contained only rudimentary or no hair shafts. A few dilated apocrine glands were found in the densely collagenized dermal connective tissue. Although the histopathologic findings were consistent with a nevus sebaceus, clinically the lesions were different. The descriptive diagnosis of sebaceous trichofollicular hamartoma was considered more appropriate.

Ocular findings in patients with the proteus syndrome include severe myopia, strabismus, coloboma, cataracts, nystagmus, and epibulbar hamartomas.⁴ The proteus syndrome was first recognized as a distinct clinical entity in 1983.² The conditions in many patients with this syndrome have probably been confused with other somatic overgrowth syndromes, particularly neurofibromatosis.⁵ We suspect that other abnormalities of the eyelid and ocular adnexa will be described as the proteus syndrome becomes more widely recognized.

References

1. Samlaska, C. P., Levin, S. W., James, W. D., Benson, P. M., Walker, J. C., and Perlik, P. C.: Proteus syndrome. *Arch. Dermatol.* 125:1109, 1989.
2. Wiedemann, H.-R., Burgio, G. R., and Aldenhoff, P.: The proteus syndrome. *Eur. J. Pediatr.* 140:5, 1983.
3. Clark, R. C., Donnai, D., Rodger, J., Cooper, J., and Baraitser, M.: Proteus syndrome. An expanded phenotype. *Am. J. Med. Genet.* 27:99, 1987.
4. Burke, J. P., Howell, R., and O'Doherty, N.: Proteus syndrome. Ocular complications. *J. Pediatr. Ophthalmol. Strabismus* 25:99, 1988.
5. Tibbles, J. A. R., and Cohen, M. M., Jr.: Proteus syndrome. The elephant man diagnosed. *Br. Med. J.* 293:683, 1986.

Ichthyosis and Crystalline Maculopathy

Michael P. Teske, M.D.,
Thomas K. Reid,
James P. Tweeten, M.D.,
and Mano Swartz, M.D.

Department of Ophthalmology, University of Utah School of Medicine. This study was supported in part by an unrestricted grant from Research to Prevent Blindness, Inc., to the Department of Ophthalmology, University of Utah School of Medicine.

Inquiries to Michael P. Teske, M.D., Department of Ophthalmology, University of Utah School of Medicine, 50 N. Medical Dr., Salt Lake City, UT 84132.

Crystalline retinopathy has been noted in a variety of conditions, including Bietti's dystrophy, cystinosis, hyperornithinemia, talc retinopathy, tamoxifen chemotherapy, canthaxanthin ingestion, primary and secondary oxalosis (methoxyflurane anesthesia, ethylene glycol ingestion, and thiamine or pyridoxine deficiency), and Sjögren-Larsson's syndrome.^{1,2} Although excessive dietary rhubarb and spinach has been suggested to cause secondary oxalosis and crystalline retinopathy,¹ we could find only reports of oxalate poisoning but not of crystalline retinopathy.

At routine ocular examination, a 44-year-old woman with a history of sporadic, congenital ichthyosis was found to have intraretinal crystals in both maculae. She reported a mild but progressive decrease in her vision during the preceding two years but denied any history of exposure to agents known to cause crystalline retinopathy. She described eating approximately six cups of both fresh spinach and rhubarb each spring. Her ocular, medical, and family history were otherwise unremarkable.

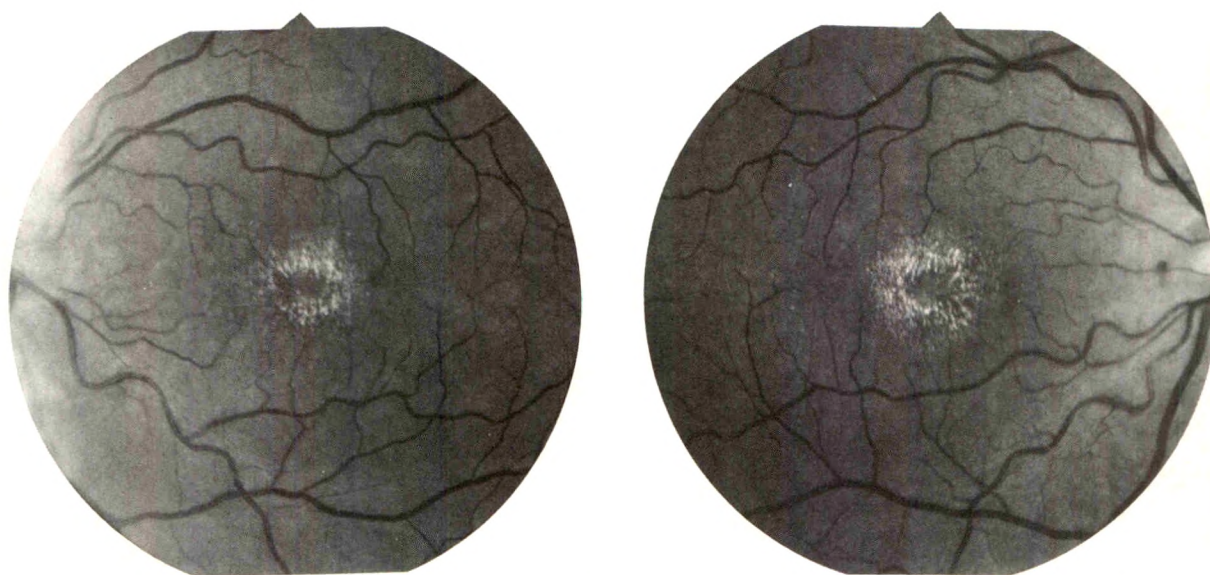


Figure (Teske and associates). Red-free fundus photographs of crystalline maculopathy in patient with lamellar ichthyosis; left eye at left; right eye at right.

Dermatologic examination confirmed the diagnosis of a mild, lamellar ichthyosis. Ocular examination disclosed best-corrected visual acuity of 20/50 in each eye. Computerized threshold perimetry and Amsler grid testing disclosed a bilateral 4-degree relative central scotoma. Color vision by Farnsworth D-15 test was normal. Her anterior segments were normal with no evidence of crystals. Ophthalmoscopy disclosed mostly superficial, and some outer, retinal crystals in a pattern of concentric rings (bull's eye) in both maculae (Figure). The crystals were mostly superficial rather than at the level of the retinal pigment epithelium, which is typical of secondary oxalosis.

Fluorescein angiography demonstrated a few mild, pericentral retinal pigment epithelial transmission defects corresponding to areas of retinal crystals. Results of laboratory tests, including electrolytes, calcium, cholesterol, liver function, complete blood cell count with differential, and 24-hour urinary oxalate levels, were all normal.

Bietti's retinopathy without corneal dystrophy, as Mauldin and O'Connor reported,¹ not associated with excessive dietary rhubarb or spinach or ichthyosis, seems an unlikely cause in our patient. Sjögren-Larsson's syndrome is an autosomal recessive congenital disorder that consists of mental retardation, lamellar ichthyosis, and spastic diplegia or tetraplegia, which

often has an associated crystalline retinopathy.³ Impaired fatty alcohol oxidation leading to accumulation of fatty alcohol in cultured skin fibroblasts has been reported as the abnormality in Sjögren-Larsson's syndrome.⁴ A clinical pathologic report described a patient reported to have Sjögren-Larsson's syndrome and glistening dots in the retina, but no abnormalities other than increased lipofuscin granules were found.⁵

The relationship between crystalline retinopathy and lamellar ichthyosis is unclear. Our otherwise normal patient may have a metabolic abnormality similar to that in Sjögren-Larsson's syndrome, resulting in both crystalline retinopathy and lamellar ichthyosis. Another possibility is an interaction between this metabolic abnormality and the high oxalate levels from her ingestion of spinach and rhubarb.

References

1. Mauldin, W. N., and O'Connor, P. S.: Crystalline retinopathy (Bietti's tapetoretinal degeneration without marginal corneal dystrophy). *Am. J. Ophthalmol.* 92:640, 1981.
2. McKeown, C. A., Swartz, M., Blom, J., and Maggiano, J. M.: Tamoxifen retinopathy. *Br. J. Ophthalmol.* 65:177, 1981.

3. Gilbert, W. R., Smith, J. L., and Nyhan, W. L.: The Sjögren-Larsson syndrome. *Arch. Ophthalmol.* 80:308, 1968.

4. Rizzo, W. B., Dammann, A. L., Craft, D. A., Black, S. H., Tilton, A. H., Africk, D., Chaves-Carballo, E., Holmgren, G., and Jagell, S.: Sjögren-Larsson syndrome. Inherited defect in the fatty alcohol cycle. *J. Pediatr.* 115:228, 1989.

5. Nilsson, S. E., and Jagell, S.: Lipofuscin and melanin content of the retinal pigment epithelium in a case of Sjögren-Larsson syndrome. *Br. J. Ophthalmol.* 71:224, 1987.

Blepharoptosis Caused by Systemic Thymoxamine

Deepak K. Chitkara, F.C. Ophth.,
and John M. Hudson, F.R.C.S.

North Riding Infirmary.

Inquiries to Deepak K. Chitkara, F.C. Ophth., North Riding Infirmary, Newport Rd., Middlesbrough, Cleveland TS1 5JE, United Kingdom.

An 84-year-old woman had a one-year history of gradual right blepharoptosis, which had become worse in the previous eight weeks. She had peripheral vascular disease, migraine, and hypertension. Her medication included atenolol, 50 mg, and thymoxamine, 40 mg twice daily. The thymoxamine was started immediately before the worsening of her symptoms of blepharoptosis.

Ocular examination showed mild dermatochalasis of both upper eyelids and a right blepharoptosis of 2 mm. The levator muscle function was 15 mm on both sides, and no fatiguability was demonstrable. The ocular movements were full, and the pupils were equal and reactive. Results of the remainder of the ocular examination were normal.

The possibility of blepharoptosis secondary to thymoxamine therapy was considered. The patient was advised to stop thymoxamine two weeks before her next appointment. The patient was examined again after four weeks. She reported a marked symptomatic improvement since discontinuing thymoxamine therapy. Clinically the blepharoptosis had resolved, although the amount of dermatochalasis and levator muscle function had remained unchanged. A two-week period of rechallenge with thymoxamine was suggested, which

would be helpful in confirming the diagnosis, but the patient refused because the condition had improved since thymoxamine had been discontinued.

The use of thymoxamine to reduce eyelid retraction is well documented.¹ Thymoxamine is a selective alpha-adrenergic blocker, which acts by competitive antagonism of noradrenaline. Systemically, it is used in short-term treatment of Raynaud's syndrome in a dose of 40 to 80 mg four times daily.² Our patient was taking 40 mg of thymoxamine twice daily for peripheral vascular disease, with little or no benefit. The British National Formulary recommends withdrawal of the drug after two weeks if no beneficial effect is noted. The side effects of systemic thymoxamine therapy include facial flushing, vertigo, headaches, mild nausea, and diarrhea.^{2,3} Topical ophthalmic solution of thymoxamine is known to cause transient ocular irritation, conjunctival hyperemia, and Horner's syndrome associated with mild blepharoptosis.⁴ Ophthalmologists use this effect of topical thymoxamine to attempt to reverse the eyelid retraction of dysthyroid ocular disease.¹ Our patient developed a clinically significant blepharoptosis after starting oral thymoxamine, and the amount of blepharoptosis was 2 mm, which is similar in degree to that noted with topical use.

Thymoxamine may cause blepharoptosis whether administered topically or systemically. This may be because of the minimal symptomatic effect it usually produces. In this patient, blepharoptosis was more noticeable because of the asymmetry in association with the increased laxity of the eyelids, which was age-related. Clinicians should be aware that systemic thymoxamine is one of the causes of drug-induced blepharoptosis.

References

1. Dixon, R. S., Anderson, R. L., and Hatt, M. U.: The use of thymoxamine in eyelid retraction. *Arch. Ophthalmol.* 97:2147, 1979.

2. Aylward, M., Bater, P. A., Davies, D. E., Dewland, P. M., Lewis, P. A., and Maddock, J.: Longterm monitoring of the effects of thymoxamine hydrochloride tablets in the management of patients with Raynaud's disease. *Curr. Med. Res. Opin.* 8:158, 1982.

3. Ward, M., and Grant, W. M.: Thymoxamine hydrochloride. An alpha-adrenergic blocker. *Surv. Ophthalmol.* 25:75, 1980.

4. Mapstone, R.: Safe mydriasis. *Br. J. Ophthalmol.* 54:690, 1970.

Vitreous Floater

Was there a blow first off?
The world strikes back;
One blow, at least, we'd all recall.
First red. A light? A bird!
Changed yellow, feathered, bright,
It swooped across my field
Canary-like.
Now, darkened to a crow,
It raven stays.

At night my crow flies down
To rest behind my lid
Till rising with the light
It swoops and glides
Across my world, all day.

One bird is not so bad.
Become familiar, like a friend,
We play.
I move my bird
To here, now here,
Then here.

But two black birds?
That's quite another thing;
I think it's hatched another;
I sense another bird.
Fledglings are often pale
Which when full-grown
Have feathers, full and black.

BERNADINE Z. PAULSHOCK, M.D.
*Medical Center of Delaware
Wilmington, Delaware*

Correspondence

Correspondence concerning recent articles or other material published in THE JOURNAL should be submitted within six weeks of publication. Correspondence must be typed double-spaced, on 8½ × 11-inch bond paper with 1½-inch margins on all four sides and should be no more than two typewritten pages in length.

Every effort will be made to resolve controversies between the correspondents and the authors of the article before publication.

The Natural Course of Central Retinal Vein Occlusion

EDITOR:

In the article, "The natural course of central retinal vein occlusion," by P. M. Quinlan, M. J. Elman, A. K. Bhatt, P. Mardesich, and C. Enger (*Am. J. Ophthalmol.* 110:118, August 1990), the authors supplied data on the visual outcome of these patients. This information contributes to the management of neovascular complications, which can be prevented in most cases by photocoagulation, and emphasizes the poor visual outcome even in patients with the nonischemic variant of this disease. We^{1,2} support their finding of an overall bad visual prognosis in a disease that Hayreh³ claimed to be benign.

The authors state that there is no treatment shown to improve vision definitely in patients with central retinal vein occlusion. We disagree; the authors do not mention controlled studies that have proven that visual improvement may follow fibrinolysis and isovolemic hemodilution.

Kohner and associates⁴ found a better visual outcome in eyes with central retinal vein occlusion in a controlled clinical trial using intravenous streptokinase. Because permanent visual loss secondary to severe vitreous hemorrhage occurred in three patients, they eliminated this treatment for the routine patient.

A second effective therapeutic is an isovolemic hemodilution.^{1,2} Bloodletting combined with replacement of lost volume by dextran 40 or hydroxyethylstarch to a hematocrit level of 0.30 to 0.35 lowers whole blood viscosity by nearly 30%. This decreases the arteriovenous filling time (from the first appearance of the dye in the retinal artery to maximal venous filling) from 17.4 to 11.6 seconds.³ Improved retinal bloodflow explains the better visual prognosis in these eyes compared to untreated eyes. Isovolemic hemodilution has been used in more than 150 patients without serious side effects.^{1,2,5} The improvement rate in our study⁶ was nearly double that of Quinlan and associates.

L. L. HANSEN, M.D.
J. WIEK, M.D.
Freiburg, Germany

References

1. Hansen, L. L., Danisevskis, P., Arntz, H. R., Hövener, G., and Wiederholt, M.: A randomized prospective study on treatment of central retinal vein occlusion by isovolemic hemodilution and photocoagulation. *Br. J. Ophthalmol.* 69:108, 1985.
 2. Hansen, L. L., Wiek, J., and Wiederholt, M.: A randomized prospective study on treatment of non-ischemic central retinal vein occlusion by isovolemic hemodilution. *Br. J. Ophthalmol.* 73:895, 1989.
 3. Hayreh, S. S.: Classification of central retinal vein occlusion. *Ophthalmology* 90:458, 1983.
 4. Kohner, E. M., Petitt, J. E., Hamilton, A. M., Bulpitt, C. J., and Dollery, C. T.: Streptokinase in central retinal vein occlusion. A controlled clinical trial. *Br. Med. J.* 1:550, 1976.
 5. Hansen, L. L., Wiek, J., Müller-Stolzenburg, N., Schade, M., and Wiederholt, M.: The effect and compatibility of isovolemic hemodilution in the treatment of ischemic and nonischemic central retinal vein occlusion. *Ophthalmologica* 199:90, 1989.
-

Treatment of Traumatic Optic Neuropathy With Corticosteroids—Correction

EDITOR:

In our article, "Treatment of traumatic optic neuropathy with corticosteroids" (*Am. J. Ophthalmol.* 110:776, December 1990), the dexamethasone dose was listed incorrectly in the footnotes to Tables 3 and 4. The correct dose, reported within the text, was 20 mg every six hours.

THOMAS C. SPOOR, M.D.
Detroit, Michigan

WALTER C. HARTEL, M.D.
Dayton, Ohio

DANIEL B. LENSINK, M.D.
MICHAEL J. WILKINSON, M.D.
Detroit, Michigan

BOOK REVIEWS

Edited by H. Stanley Thompson, M.D.

Manual of Visual Fields. Edited by Elliot B. Werner. New York, Churchill Livingstone, Inc., 1990. Softcover, 238 pages, index, illustrated. \$39

Reviewed by WILLIAM M. HART, JR.
St. Louis, Missouri

Residents in ophthalmology have always needed a convenient source of information for the theory and practice of clinical perimetry. As its name implies, this manual seeks to fill that role. Edited by Elliot Werner with contributions by Drs. Chauhan, LeBlanc, and Mills, the 12 chapters of the text deal initially with the historical background of clinical perimetry and the rapid development over the past two decades of sophisticated forms of manual and automated visual field testing. The principal instruments discussed include the Goldmann perimeter (the gold standard of manual perimeters) and the two dominant automated instruments, the Octopus perimeter and the family of Humphrey perimeters (referred to as visual field analyzers). The rudiments of the technical use of these instruments and an introduction to the more basic elements of visual psychophysics used in clinical visual field testing are covered in turn. After a general discussion of the physiology of the normal visual field, separate chapters are devoted to diseases of the retina and choroid, glaucoma, the optic nerve, the chiasm, and the retrochiasmal visual pathways.

One gets a sense of day-to-day perimetry from the clinical examples of various types of visual field defects. These examples seem to represent the kind of problems commonly encountered in ophthalmic practices. There is a good explanation of the common artifacts of perimetry, including those caused by small pupils, poor patient performance, malalignment of the patient's head in the instrument, and the like.

This text is not meant to be an exhaustive reference text; it is a reasonably complete introduction to perimetry for trainees that are new to the game. Its softbound format and moderate cost will make it attractive to many.

Books Received

Age-Related Cataract. By Richard W. Young. New York, Oxford University Press, 1990. 290 pages, index. \$55

Dr. Young has a long-standing interest in the causes of cataract. He has recently reviewed approximately 1,000 publications on the subject and has reached a conclusion so simple that it is not easy to swallow in one gulp. Dr. Young insists with some vigor that the onset of cataracts could be significantly delayed if we all were to use protective eye wear that would keep the ultraviolet light out of our eyes.

Practical Management of Squint. By Graham Pittar. Australia, Turton & Armstrong Pty. Ltd., 1990. 341 pages, index, illustrated. \$147

Dr. Pittar's book contains some provocative reading for the ophthalmologist interested in strabismus. The author emphasizes and explains his simplified approach to patient examination.

The Book List

The Eye in Systemic Disease, ed. 2. By Jack J. Kanski and Dafydd J. Thomas. Stoneham, Butterworths, 1990. 161 pages, index, illustrated. \$80

Orthoptic Assessment and Management. By David Stidwill. St. Louis, Mosby-Year Book, Inc., 1990. 182 pages, index, illustrated. \$59.95

Phacoemulsification Surgery. Edited by Terence M. Devine and William Banko. New York, Pergamon Press, 1990. 130 pages, index, illustrated. \$125

ABSTRACT DEPARTMENT

Edited by Michael A. Kass, M.D.

Ticlopidine treatment reduces the progression of nonproliferative diabetic retinopathy. Ticlopidine Microangiography of Diabetes Study Group*. Arch. Ophthalmol. 108:1577, 1990.

DIABETIC RETINOPATHY, TICLOPIDINE, FLUORESCEIN ANGIOGRAPHY

This randomized, double-masked, placebo-controlled trial assessed the effect of ticlopidine, an antiplatelet agent, in reducing the progression of nonproliferative diabetic retinopathy in 435 patients followed up for three years. The mean yearly increase in definite microaneurysms on fluorescein angiograms was significantly higher ($P = .03$) in the placebo group (1.44 ± 4.67) than in the ticlopidine group (0.48 ± 5.79). Significance was limited to primary analysis using a quality angiographic coefficient for definite microaneurysms in patients with at least three readable angiograms over a three-year period. Ticlopidine induced a sevenfold reduction of the yearly microaneurysm progression (0.23 ± 6.66) in treated diabetic patients compared with the placebo (1.57 ± 5.29) ($P = .03$). Fewer insulin-treated diabetic patients developed new vessels in the ticlopidine group than in the placebo group, (borderline statistical significance, $P = .056$). Overall retinopathy progression was significantly less severe in the ticlopidine group ($P = .04$). The study demonstrated that ticlopidine slowed the progression of nonproliferative diabetic retinopathy.—Michael A. Kass

*Jacques Mirouze, M.D., Clinique des Maladies Métaboliques et Endocriniennes, Hôpital Lapeyronie, 34059 Montpellier, France.

Slow glucose removal rate and hyperinsulinemia precede the development of type II diabetes in the offspring of diabetic parents. Warram, J. H.*, Martin, B. C., Krolewski, A. S., Soeldner, J. S., and Kahn, C. R.: Ann. Intern. Med. 113:909, 1990.

TYPE II DIABETES, REDUCED GLUCOSE CLEARANCE, COMPENSATORY HYPERINSULINEMIA

There is debate concerning whether insulin resistance or insulin deficiency is the primary defect of type II diabetes. Intravenous glucose tolerance tests were performed on 155 nondiabetic offspring (age range, 16 to 60 years) who had two parents with type II diabetes and 186 nondiabetic control subjects in the same age range who had no family history of diabetes. Two characteristics distinguished the offspring of diabetic parents from control subjects. The offspring of diabetic parents had slower glucose removal rates and higher insulin levels (fasting and during the second phase of insulin response to intravenous glucose) than did control subjects, even after adjustment for differences in obesity. Type II diabetes developed in 16% of the offspring of diabetic parents. The mean glucose removal rate at baseline was 1.7%/min among offspring who subsequently developed diabetes, 2.2%/min among offspring who remained nondiabetic, and 2.3%/min among control subjects. Corresponding means for first-phase insulin were 498, 354, and 373 pM, respectively, whereas second-phase insulin means were 329, 117, and 87 pM, respectively. It appears that reduced glucose clearance is present one to two decades before type II diabetes is diagnosed. This reduced glucose clearance is accompanied by compensatory hyperinsulinemia, not hypoinsulinemia, which suggests that the primary defect is in peripheral tissue response to insulin and glucose, not in the pancreatic beta cells.—Michael A. Kass

*Section on Epidemiology and Genetics, Research Division, Joslin Diabetes Center, One Joslin Place, Boston, MA 02215.

Cerebral glucose metabolism in adults with hyperactivity of childhood onset. Zametkin, A. J.*, Nordahl, T. E., Gross, M., King, A. C., Semple, W. E., Rumsey, J., Hamburger, S., and Cohen, R. M.: N. Engl. J. Med. 323:1361, 1990.

HYPERACTIVITY, GLOBAL AND REGIONAL CEREBRAL GLUCOSE METABOLISM

The cause of childhood hyperactivity is unknown. One hypothesis is that altered cerebral glucose metabolism is responsible for hyperactivity. Twenty-five hyperactive individuals, parents of hyperactive children who continued to have symptoms into adulthood, underwent measurements of cerebral glucose metabolism by positron emission tomography. Fifty normal adults served as a control group. Global cerebral glucose metabolism was 8.1% lower in the adults with hyperactivity than in the normal control subjects (mean \pm standard deviation, 9.05 ± 1.20 mg per minute per 100 g in the adults with hyperactivity versus 9.85 ± 1.68 mg per minute per 100 g in the control subjects, $P = .034$). In the adults with hyperactivity, glucose metabolism was significantly reduced in 30 of 60 specific brain regions when compared to normal control subjects. The greatest reductions in glucose metabolism were in the premotor cortex and the superior prefrontal cortex, areas shown to be involved in the control of attention and motor activity.—Michael A. Kass

*Section on Clinical Brain Imaging, National Institute of Mental Health, NIH, Bldg. 10 4N317, 9000 Rockville Pike, Bethesda, MD 20892.

Vision despite tomographic absence of the occipital cortex. Summers, C. G.*, and MacDonald, J. T.: *Surv. Ophthalmol.* 35:188, 1990.

MICROCEPHALY, ABSENCE OF OCCIPITAL CORTEX, FUNCTIONING VISION

Complex visual processing in humans is thought to depend upon the geniculostriate cortex. Patients with acquired lesions of the occipital cortex often have severe limitations of visual function and may be cortically blind. A 14-month-old boy had microcephaly, spastic diplegia, and esotropia. The child reached for objects and held them in the midline, and he could fix monocularly and follow brightly colored targets measuring approximately 3 cm. Pupillary reactions were normal. A tomographic scan of the head disclosed absence of normal occipital cortex, and electroencephalography

showed markedly reduced voltages over the occipital region. It is possible that visual functioning in this patient was related to a more primitive nonstriate visual system that exists in other primates. This study indicates that visual function cannot be predicted when severe developmental anomalies of the occipital cortex are detected with computed tomography.—Michael A. Kass

*Department of Ophthalmology, University of Minnesota, Box 493 UMHC, 516 Delaware St. S.E., Minneapolis, MN 55455.

The opposite pupil in herniation. Ropper, A. H.*: *Neurology* 40:1707, 1990.

TRANSTENTORIAL HERNIATION, CONTRALATERAL PUPIL ABNORMALITIES

Pupillary dilation is a well-known sign of a herniating mass. Most of the published studies describe only the pupil on the side of the mass, although there have been a few descriptions of late dilation of the opposite pupil in uncus herniation. Serial examinations were performed on 13 patients with transtentorial herniation. In most patients, the contralateral pupil was initially 2.5 to 4.0 mm in diameter and had a reduced light reaction. This was followed by a slight reduction in the size of the contralateral pupil and then by the contralateral pupil becoming larger than its original size. Subsequent deterioration varied, but eventually the ipsilateral and contralateral pupils were fixed and dilated. These observations suggest that once transtentorial herniation causes dilation of the pupil on the ipsilateral side, subsequent deterioration may be monitored through changes in reactivity and size of the opposite pupil.—Michael A. Kass

*St. Elizabeth's Hospital, 736 Cambridge St., Boston, MA 02135.

Why are eye muscles frequently involved in myasthenia gravis? Kaminski, H. J.*, Mass,

E., Spiegel, P., and Ruff, R. L.: Neurology 40:1663, 1990.

MYASTHENIA GRAVIS, EXTRAOCULAR MUSCLE INVOLVEMENT

Extraocular muscle involvement occurs in approximately 90% of individuals with myasthenia gravis at the onset of the disease. At least 15% of patients with myasthenia gravis manifest only ocular signs. The authors hypothesize that certain properties of the extraocular muscles may predispose them to involvement in myasthenia gravis. First, slight extraocular muscle weakness can misalign the visual axes sufficiently to produce symptoms. Second, the high firing frequencies of extraocular muscle motor units may increase their susceptibility to fatigue. In myasthenia gravis, antibodies directed at nicotinic acetylcholine receptors reduce acetylcholine at the neuromuscular junction and impair muscular excitation. The physiologic properties of extraocular muscle fibers may make them uniquely susceptible to this block of neuromuscular excitation. Neuromuscular epitopes unique to extraocular muscle may exist, and thus antibodies in some patients with myasthenia gravis could be targeted specifically to extraocular muscle postsynaptic membranes.—Michael A. Kass

*Neurology Service 141A7(W), Cleveland Veterans Affairs Medical Center, 10701 East Blvd., Cleveland, OH 44106.

In vivo and in vitro collagenolytic activity of *Acanthamoeba castellanii*. He, Y. G., Niederkorn, J. Y.*, McCulley, J. P., Stewart, G. L., Meyer, D. R., Silvany, R., and Dougherty, J.: Invest. Ophthalmol. Vis. Sci. 31:2235, 1990.

ACANTHAMOEBA CASTELLANII, COLLAGENOLYTIC ENZYME

Axenic cultures of *Acanthamoeba castellanii* contained a collagenolytic enzyme that digested collagen shields and purified collagen in vitro. Specificity of biologic activity was determined by the addition of selected enzyme in-

hibitors to the assays and revealed that the parasite-conditioned medium contained both collagenase and lower concentrations of other proteolytic enzymes. However, most of the collagenolytic and pathogenic activity was directly attributable to specific collagenase. Intrastromal injection of sterile, *Acanthamoeba*-conditioned culture medium into naive Lewis rats produced corneal lesions clinically similar to and closely resembling those found in biopsy specimens of human patients diagnosed with acanthamoebic keratitis. Histopathologic analysis revealed moderate-to-severe neutrophil infiltration, disruption of stromal lamellae, and edema. Identical pathologic sequelae were produced by intrastromal injection of purified collagenase (25 units/ml). The pathogenicity of the soluble parasite-derived product was removed by passage over affinity columns armed with antibody specific for collagenase. These results indicated that soluble parasite-derived factors were capable of producing lesions characteristic of acanthamoebic keratitis and that the pathogenicity of these factors was either directly or indirectly attributable to specific collagenase activity.—Authors' abstract

*Department of Ophthalmology, University of Texas Southwestern Medical Center at Dallas, Dallas, TX 75235.

Antibodies to Epstein-Barr virus in iridocorneal endothelial syndrome. Tsai, C. S., Ritch, R.*, Straus, S. E., Perry, H. D., and Hsieh, F. Y.: Arch. Ophthalmol. 108:1572, 1990.

IRIDOCORNEAL ENDOTHELIAL SYNDROME, EPSTEIN-BARR VIRUS

Antibody titers to Epstein-Barr virus were determined in 13 patients with iridocorneal endothelial syndrome and in 13 healthy race-, age-, and sex-matched controls. Both the geometric mean titer of IgG antibodies to the Epstein-Barr virus capsid antigen and the proportion with high titers of IgG antibodies to the Epstein-Barr virus capsid antigen ($\geq 1:640$) were significantly higher in 12 seropositive patients with iridocorneal endothelial syndrome

than in 12 seropositive controls (1/761:1/202, $P = .001$; 83.3%:8.3%, $P < .001$). Ten of 12 seropositive patients with iridocorneal endothelial syndrome and five of 12 seropositive controls had antibodies to Epstein-Barr virus-induced early antigens ($\geq 1:10$) (Fisher's Exact Test, $P < .05$), while four seropositive patients with iridocorneal endothelial syndrome and one seropositive control had low to undetectable levels of antibodies to Epstein-Barr virus-associated nuclear antigen ($\leq 1:5$) ($P > .1$). Antibody levels to cytomegalovirus or measles virus were not different between patients with iridocorneal endothelial syndrome and controls. Additional studies showed no evidence of humoral immune disorder or collagen vascular disease in the patients with iridocorneal endothelial syndrome. The serologic profiles suggest that the patients with iridocorneal endothelial syndrome examined had a cellular immune abnormality sufficient to permit reactivation of latent Epstein-Barr virus infection and imply, but do not establish, a role for Epstein-Barr virus infection in the pathogenesis of some cases of the iridocorneal endothelial syndrome.—Authors' abstract

*Glaucoma Service, New York Eye and Ear Infirmary, 310 E. 14th St., New York, NY 10003.

Relation of meat, fat, and fiber intake to the risk of colon cancer in a prospective study among women. Willett, W. C.*, Stampfer, M. J., Colditz, G. A., Rosner, B. A., and Speizer, F. E.: N. Engl. J. Med. 323:1664, 1990.

INCIDENCE OF COLON CANCER, ANIMAL FAT INTAKE

The rate of colon cancer in various countries is correlated with the per capita consumption of red meat and animal fat. Colon cancer developed in 150 of 88,751 women, aged 34 to 59 years, who did not have a history of cancer, inflammatory bowel disease, or familial polyposis. After adjustment for total energy intake, animal fat intake was associated positively with the risk of colon cancer ($P = .01$). The relative risk for the highest quintile of fat consumption as compared to the lowest quintile was 1.89

(95% confidence interval, 1.13 to 3.15). No association was found between colon cancer and vegetable fat intake. The relative risk of colon cancer in women who ate beef, pork, or lamb as a main dish every day was 2.49 (95% confidence interval, 1.24 to 5.03), as compared with those reporting consumption of less than once a month. Consumption of processed meats and liver was also significantly associated with increased risk, whereas consumption of fish and chicken without skin was related to decreased risk. A low intake of fiber from fruits appeared to contribute to the risk of colon cancer, but this relationship was not statistically independent of meat intake. These data support the hypothesis that a high intake of animal fat increases the risk of colon cancer, and they support existing recommendations to substitute fish and chicken for meats high in fat.—Michael A. Kass

*Channing Laboratory, Department of Medicine, Harvard Medical School, Boston, MA.

A controlled trial of early adjunctive treatment with corticosteroids for *Pneumocystis carinii* pneumonia in the acquired immunodeficiency syndrome. Bozzette, S. A.*, Sattler, F. R., Chiu, J., Wu, A. W., Gluckstein, D., Kemper, C., Bartok, A., Niosi, J., Abramson, I., Coffman, J., Hughlett, C., Loya, R., Cassens, B., Akil, B., Meng, T.-C., Boylen, C. T., Nielsen, D., Richman, D. D., Tilles, J. G., Leedom, J., McCutchan, J. A., and the California Collaborative Treatment Group: N. Engl. J. Med. 323:1451, 1990.

PNEUMOCYSTIS CARINII PNEUMONIA, CORTICOSTEROID TREATMENT

Pneumocystis carinii pneumonia is a common cause of serious morbidity and mortality in patients with the acquired immunodeficiency syndrome. A total of 333 patients with AIDS and *Pneumocystis* pneumonia received standard treatment and were randomly assigned to receive either corticosteroids (beginning with the equivalent of 40 mg of prednisone twice daily) or no additional therapy. The primary end points in this unmasked trial were the occurrence of respiratory failure, death, and dose-limiting toxicity of the initial standard therapy.

The patients assigned to treatment with corticosteroids had a lower cumulative risk at 31 days of respiratory failure (0.14 versus 0.30, $P = .004$) and of death (0.11 versus 0.23, $P = .009$), as well as a lower risk of death within 84 days (0.16 versus 0.26, $P = .026$). The frequency of dose-limiting toxicity of the standard therapy was similar in the two treatment groups. Clinical benefit could not be demonstrated, however, for patients with mild disease. Thus it appears that early adjunctive treatment with corticosteroids reduces the risks of respiratory failure and death in patients with AIDS and moderate to severe *Pneumocystis* pneumonia. Because the adverse effects are few, corticosteroids should be included as part of the initial treatment for persons with AIDS who have moderate to severe *Pneumocystis* pneumonia.—Michael A. Kass

*Division of Infectious Diseases, Box H208, University of California—San Diego Medical Center, 225 Dickinson St., San Diego, CA 92103.

Diclofenac-associated hepatotoxicity. Helfgott, S. M., Sandberg-Cook, J., Zakim, D., and Nestler, J.*: JAMA 264:2660, 1990.

DICLOFENAC SODIUM, HEPATITIS, HEPATIC NECROSIS

Diclofenac sodium (Voltaren), a noncorticosteroidal antiinflammatory drug that is a phenylacetic acid derivative, has recently been released for use in the United States. Seven patients who received the drug developed significant hepatitis. Signs and symptoms developed within several weeks of starting the drug and generally resolved four to six weeks after discontinuation of the drug. The only patient rechallenged with diclofenac developed a recurrence of the hepatic abnormalities. In one patient fatal fulminant hepatitis developed despite early withdrawal of the drug. Three previous fatalities associated with diclofenac therapy have been reported. It is unclear whether the incidence of hepatotoxicity is higher with this drug compared with other noncorticosteroidal antiinflammatory drugs. Careful

patient monitoring is advised, and prompt discontinuation of the drug is suggested when signs or symptoms of liver disease develop.—Michael A. Kass

*85 Seymour St., Hartford, CT 06106.

A public hospital closes. Impact on patients' access to care and health status. Bindman, A. B.*, Keane, D., and Lurie, N.: JAMA 264:2899, 1990.

PUBLIC HOSPITAL CLOSING, AVAILABILITY OF MEDICAL CARE, PATIENTS' HEALTH STATUS

The authors surveyed the health status and access to medical care of individuals from Shasta County, California, who had been medical inpatients at Shasta General Hospital in the year before it closed, and compared them with individuals from San Luis Obispo County, whose public hospital did not close. Surveys were made after the closing of Shasta General Hospital and one year later. The medical outcomes were assessed using the Medical Outcomes Study Short Form and a series of transition questions that asked about changes in health over time. Data were available for 88% of patients at one year, 219 from Shasta County and 195 from San Luis Obispo County. At the follow-up, the percentage of patients from Shasta County who reported no regular health care provider increased from 14.0% to 27.7%, and the percentage who reported they were denied care increased from 10.8% to 16.9%. In contrast, patients in San Luis Obispo County reported improved access to a regular health care provider, and the level of denied care was unchanged. Patients in Shasta County had significant declines in health perception, social and role function, and increases in pain as compared with the patients in San Luis Obispo County. Thus, closing of a public hospital had a significant impact on access to health care and was associated with a decline in perceived health status.—Michael A. Kass

*Department of Medicine, San Francisco General Hospital, 1001 Potrero Ave., Rm. 5H-22, San Francisco, CA 94110.

Use of high dose chloral hydrate for ophthalmic exams in children. A retrospective review of 302 cases. Fox, B. E. S., O'Brien, C. O., Kangas, K. J., Murphree, A. L., and Wright, K. W.*: J. Pediatr. Ophthalmol. Strabismus 27:242, 1990.

CHLORAL HYDRATE, EXAMINATION OF CHILDREN

A careful study of the safety and effectiveness of chloral hydrate is lacking, although chloral hydrate sedation has been proposed as an alternative to examination under anesthesia for pediatric patients who cannot cooperate with routine test procedures. A cohort of 302 patients between the ages of 1 month and 5 years received high-dose chloral hydrate for ophthalmic examination. The patients had nothing to eat or drink for four hours before drug administration. The patients then received chloral hydrate, 80 to 100 mg/kg of body weight, with a maximum dose of 3 g. Supplemental administration of chloral hydrate, when required, was one half of the original dose. The patients were monitored during sedation and until fully awake. Good sedation without the need for supplemental doses was attained in 266 of 302 patients (88%). There were no complications, including emesis, respiratory distress or depression, behavioral problems, changes in vital signs, patient injury, or hospital admission. The high dose of chloral hydrate resulted in safe and generally successful sedation of pediatric patients for ophthalmic examination.—Michael A. Kass

*Division of Ophthalmology, Childrens Hospital Los Angeles, 4650 Sunset Blvd., Los Angeles, CA 90027.

A randomized, prospective field trial of a conjugate vaccine in the protection of infants and young children against invasive *Haemophilus influenzae* type b disease. Eskola, J.*, Käyhty, H., Takala, A. K., Peltola, H., Rönberg, P.-R., Kela, E., Pekkanen, E., McVerry, P. H., and Mäkelä, P. H.: N. Engl. J. Med. 323:1381, 1990.

HAEMOPHILUS INFLUENZAE, POLYSACCHARIDE-PROTEIN CONJUGATE VACCINE

Haemophilus influenzae type b is the leading cause of invasive bacterial disease in young children. Unfortunately the capsular polysaccharide vaccine does not protect children under the age of 18 months, who are at greatest risk for developing the disease. In a prospective randomized trial, 114,000 infants in Finland received *H. influenzae* type b capsular polysaccharide-diphtheria toxoid conjugate vaccine. Children born on odd-numbered days were vaccinated at the ages of 3, 4, 6, and 14 to 18 months; children born on even-numbered days formed the control group and received the same vaccine at the age of 24 months. There were four cases of verified bacteremic *H. influenzae* type b disease in the group receiving early vaccination, as compared to 64 cases in the control group receiving late vaccination. No serious adverse effects of the vaccine were reported. This study suggests that a new conjugate vaccine consisting of the capsular polysaccharide of *H. influenzae* type b linked covalently to a protein carrier, administered to infants beginning at the age of 3 months, is highly effective in protecting young children against invasive *H. influenzae* type b infections.—Michael A. Kass

*National Public Health Institute, Mannerheimintie 166, SF-00300 Helsinki, Finland.

Quantitative analysis of retinal hemodynamics using targeted dye delivery. Guran, T., Zeimer, R. C.*, Shahidi, M., and Mori, M. T.: Invest. Ophthalmol. Vis. Sci. 31:2300, 1990.

TARGETED DYE DELIVERY, LASER RELEASE, RETINAL HEMODYNAMICS

A new method designed to allow repeated mapping of retinal hemodynamics on a macro- and microcirculatory level was evaluated in the primate eye. The method, called "targeted dye delivery," consists of encapsulating a fluorescent dye in temperature-sensitive liposomes, injecting the liposomes systemically, and using a light pulse from an argon laser to release a bolus of dye in a targeted retinal vessel. The follow-up of the well-defined dye front thus generated allows calculation of the blood flow and capillary transit time. Evaluation of tar-

geted dye delivery in a monkey indicated that centerline blood velocity and the vessel diameter can be measured with a reproducibility of 10% and 4%, respectively, in vessels that are 40 μm and larger. These measurements yielded flow values that had a reproducibility of 10% on the same day and 13% on different days. The normalization of flow rate by the vessel diameter was consistent with theoretic estimates and promises to be a circulation indicator independent of variations between individual and species. The transit time across capillary beds at different locations was found to be similar, thus indicating that the method could be used to evaluate the local viability of the microcirculation.—Authors' abstract

*UIC Eye Center, Applied Physics Laboratory, Department of Ophthalmology, 1855 W. Taylor St., Chicago, IL 60612.

Synthetic analogues of fumagillin that inhibit angiogenesis and suppress tumor growth.

Ingber, D.*, Fujita, T., Kishimoto, S., Sudo, K., Kanamaru, T., Brem, H., and Folkman, J.: *Nature* 348:555, 1990.

NEOVASCULARIZATION, ANGIOGENESIS INHIBITORS, FUMAGILLIN

Neovascularization is critical for the growth of tumors and is a dominant feature in a variety of angiogenic diseases such as diabetic retinopathy, hemangiomas, arthritis and psoriasis. Recognition of the potential therapeutic benefit of controlling unabated capillary growth has led to a search for safe and effective angiogenesis inhibitors. We report here the synthesis of a family of novel inhibitors that are analogues of fumagillin, a naturally secreted antibiotic of *Aspergillus fumigatus* fresenius. We first isolated this fungus from a contaminated culture of capillary endothelial cells. Purified fumagillin inhibited endothelial cell proliferation in vitro and tumor-induced angiogenesis in vivo; it also inhibited tumor growth in mice, but prolonged administration was limited because it caused severe weight loss. Synthesis of fumagillin analogues yielded potent angiogenesis inhibitors ("angioinhibins") which suppress the growth

of a wide variety of tumors with relatively few side-effects.—Authors' abstract

*Department of Surgery, The Children's Hospital, Boston, MA 02115.

Central venous stasis retinopathy following the use of tranexamic acid. Snir, M.*, Axer-Siegel, R., Buckman, G., and Yassur, Y.: *Retina* 10:181, 1990.

TRANEXAMIC ACID, ANTIFIBRINOLYTIC AGENT, VENOUS STASIS RETINOPATHY

Tranexamic acid is an antifibrinolytic drug that is a competitive inhibitor of plasminogen activation and a noncompetitive inhibitor of plasmin. Its antifibrinolytic action facilitates thrombosis formation and protects preexisting thrombi. Tranexamic acid has been clinically effective in a number of conditions, including urinary tract bleeding, gastrointestinal hemorrhage, recurrent epistaxis, and after dental or general surgery in patients with hemophilia. One of the most frequent indications for the use of the drug is in the management of menorrhagia. Two women, 38 and 40 years of age, respectively, developed blurred vision in one eye after treatment with tranexamic acid for menorrhagia. Both patients had taken the drug for approximately one week. Neither patient had other clinical or laboratory risk factors for thrombotic disease. Both patients had central retinal venous stasis with disk edema, engorged veins, cotton-wool spots, and hemorrhages. Fluorescein angiography disclosed delayed venous filling and dilated capillaries as well as profuse leakage from the disk and the veins. In both cases tranexamic acid therapy was stopped, and the patients were treated with systemic corticosteroids and dipyridamole, 225 mg/day. Within ten days there was regression of the papilledema, hemorrhages, and exudates. Both patients eventually recovered 20/20 visual acuity. Tranexamic acid has been reported to cause other thrombotic disorders, and it appears likely that the drug is causally

linked to the venous stasis retinopathy in these patients.—Michael A. Kass

*Department of Ophthalmology, Beilinson Medical Center, 49 100 Petah Tikva, Israel.

Nitric oxide. A novel signal transduction mechanism for transcellular communication.
Ignarro, L. J.*: Hypertension 16:477, 1990.

NITRIC OXIDE, CYCLIC GUANOSINE
MONOPHOSPHATE, VASODILATORS, MODULATOR
OF VASCULAR SMOOTH MUSCLE TONE AND
PLATELET FUNCTION

Nitric oxide first captured the interest of biologists when this inorganic molecule was found to activate cytosolic guanylate cyclase and stimulate cyclic guanosine monophosphate (GMP) formation in mammalian cells. Further studies led to the finding that nitric oxide causes vascular smooth muscle relaxation and inhibition of platelet aggregation by mechanisms involving cyclic GMP and that several clinically used nitrovasodilators owe their biological actions to nitric oxide. Nitric oxide possesses physicochemical and pharmacological properties that make it an ideal candidate for a short-term regulator or modulator of vascular smooth muscle tone and platelet function. Nitric oxide is synthesized by various mammalian tissues including vascular endothelium, macrophages, neutrophils, hepatic Kupffer cells, adrenal tissue, cerebellum, and other tissues. Nitric oxide is synthesized from endogenous L-arginine by a nitric oxide synthase system that possesses different cofactor requirements in different cell types. The nitric oxide formed diffuses out of its cells of origin and into nearby target cells, where it binds to the heme group of cytosolic guanylate cyclase and thereby causes enzyme activation. This interaction represents a novel and widespread signal transduction mechanism that links extracellular stimuli to the biosynthesis of cyclic GMP in nearby target cells. The small molecular size and lipophilic nature of nitric oxide enable communication with nearby cells containing cytosolic guanylate cyclase. The extent of transcellular communica-

tion is limited by the short half-life of nitric oxide, thereby ensuring a localized response. Labile nitric oxide-generating molecules such as S-nitrosothiols may be involved as precursors or effectors. Further research will provide a deeper understanding of the biology of nitric oxide and the nature of associated pathophysiological states.—Author's abstract

*Department of Pharmacology, UCLA School of Medicine, CHS, Los Angeles, CA 90024.

Regional myocardial metabolism of high-energy phosphates during isometric exercise in patients with coronary artery disease.
Weiss, R. G., Bottomley, P. A.*, Hardy, C. J., and Gerstenblith, G.: N. Engl. J. Med. 323:1593, 1990.

MYOCARDIAL METABOLISM, EXERCISE TESTING,
PHOSPHORUS 31 NUCLEAR MAGNETIC
RESONANCE IMAGING

The maintenance of cellular levels of high-energy phosphates is required for myocardial function and preservation. In animals, severe myocardial ischemia is characterized by the rapid loss of phosphocreatine and a decrease in the ratio of phosphocreatine to adenosine triphosphate. To determine whether ischemic metabolic changes are detectable in humans, spatially localized phosphorus 31 nuclear magnetic resonance spectra were recorded from the anterior myocardium before, during, and after isometric hand-grip exercise. The mean ratio of phosphocreatine to adenosine triphosphate in the left ventricular wall when subjects were at rest was 1.72 ± 0.15 in normal subjects and 1.59 ± 0.31 in subjects with nonischemic heart disease. The ratio did not change during hand-grip exercise in either group. In patients with coronary heart disease and ischemia caused by severe stenosis of the left anterior descending or left main coronary arteries, however, the ratio decreased from 1.45 ± 0.31 at rest to 0.91 ± 0.24 during exercise ($P < .001$) and recovered to 1.27 ± 0.38 two minutes after exercise. Repeat exercise testing in five patients after

revascularization yielded values of 1.60 ± 0.20 at rest and 1.62 ± 0.18 during exercise, as compared with 1.51 ± 0.19 at rest and 1.02 ± 0.26 during exercise before revascularization. The decrease in the ratio of phosphocreatine to adenosine triphosphate during hand-grip exercise in patients with myocardial ischemia reflects a transient imbalance between oxygen supply and demand in myocardium with com-

promised blood flow. Exercise testing with phosphorus 31 nuclear magnetic resonance imaging is a useful method for assessing the effect of ischemia on myocardial metabolism of high-energy phosphates and for monitoring the response to treatment.—Michael A. Kass

*General Electric Research and Development Center, P.O. Box 8, Schenectady, NY 12301.

NEWS ITEMS

Send News Items to
American Journal of Ophthalmology
435 N. Michigan Ave., Suite 1415
Chicago, IL 60611

The Journal invites readers to submit announcements concerning meetings, postgraduate courses, lectures, honors, and appointments. Each item must be typed double-spaced on bond paper with 1½-inch margins. Only one news item should be submitted on each page. Announcements concerning meetings and courses must contain the title, location, dates, sponsors, and address required for additional information. Each item must not exceed 75 words in length and be prepared in narrative, not outline, form. Announcements of meetings and courses must be received at least four months before the event.

Centro de Oftalmologia Barraquer: Novel Advances in Cataract and Corneal Refractive Surgery

The 50th Anniversary of the Centro de Oftalmologia Barraquer: Novel Advances in Cataract and Corneal Refractive Surgery will be held Sept. 8 and 9, 1991, in Barcelona, Spain. For further information, write Instituto Barraquer, Laforja, 88, E-08021 Barcelona, Spain; fax 34-3-200-24-69.

International Symposium of Ophthalmic Plastic Surgery

The International Symposium of Ophthalmic Plastic Surgery will hold a meeting, Palpebral, Lacrimal, and Orbital Surgery: Problems and Complications, June 7 and 8, 1991, in Nice, France. For additional information, write P. Ritleng, 10 rue du Congres, 06000 Nice, France; fax 93-82-32-30.

Turkish Ophthalmological Society: International Summer Symposium

The Turkish Ophthalmological Society will hold its International Summer Symposium, Capsular Surgery, June 7 and 8, 1991, in Izmir, Turkey. For further information, write Mahmut Kaskaloglu, M.D., Talatpasa Blvd., 58/4, Alsancak, Izmir, Turkey; fax 90-51-191682.

Case Western Reserve University School of Medicine: Neuro-Ophthalmology 1991

Case Western Reserve University School of Medicine: Neuro-Ophthalmology 1991 will be held June 7, 1991, in Cleveland, Ohio. For further information, write John Rus, Office of Continuing Medical Education, 2109 Adelbert

Rd., W-175, Cleveland, OH 44106; telephone (216) 368-2409.

The Cleveland Clinic Foundation: 20th Annual Department Symposium on Ocular, Adnexal and Orbital Infection and Inflammatory Diseases

The Cleveland Clinic Foundation, 20th Annual Department Symposium on Ocular, Adnexal and Orbital Infection and Inflammatory Diseases, will be held June 14 and 15, 1991. For further information, write Rose Mary Fitzgerald, Department of Continuing Education, Cleveland Clinic Foundation, P.O. Box 94977, Cleveland, OH 44195-5241; telephone (216) 444-5696 or (800) 762-8173.

University of Louisville School of Medicine: C. Dwight Townes Memorial Seminar

The University of Louisville School of Medicine will hold its 19th C. Dwight Townes Memorial Seminar at the University of Louisville on May 10 and 11, 1991. The Townes speaker will be Norman Jaffe. For further information, write Nancy Rodman, 301 E. Muhammad Ali Blvd., Louisville, KY 40202; telephone (502) 588-5466.

Long Island Jewish Medical Center: A Clinical Day in Ophthalmology

The Long Island Jewish Medical Center and North Shore University will sponsor A Clinical Day in Ophthalmology—Neuro-Ophthalmology Problems: Surgical Solutions, May 22, 1991, at the Holiday Inn Crowne Plaza (LaGuardia Airport) in East Elmhurst, New York. For further information, write Ann J. Boehme, Associate Director of Continuing Education, Long Island Jewish Medical Center, New Hyde Park, NY 11042; telephone (718) 470-8650.

Manhattan Eye, Ear & Throat Hospital: Ophthalmology Alumni Symposium

The Department of Ophthalmology of the Manhattan Eye, Ear & Throat Hospital will hold its Alumni Symposium at the Waldorf Astoria in New York City, May 10 and 11, 1991. For further information, write Kimberly Corbin, Dept. of Ophthalmology, Manhattan Eye, Ear & Throat Hospital, 210 E. 64th St., New York, NY 10021; telephone (212) 605-3761.



Mayo Foundation: Ophthalmic Reviews

The Mayo Foundation will sponsor Ophthalmic Reviews with emphasis on surgical and medical management of the cornea and external disease problems including keratorefractive surgery and high-risk cataract extraction, May 10 and 11, 1991, in Rochester, Minnesota. For additional information, write Bonita Walin, Postgraduate Courses, Section of Continuing Education, Mayo Foundation, Rochester, MN 55905; telephone (507) 284-2509 or (800) 323-2688.

University of Missouri-Kansas City School of Medicine: Didactic Wet Laboratory and Excimer Laser Course

The University of Missouri-Kansas City School of Medicine will hold a Didactic Wet Laboratory and an Excimer Laser Course with a clinical update on retinal laser therapy at the Eye Foundation of Kansas City on June 7 and 8, 1991. For further information, write John W. Irvine, M.D., The Eye Foundation of Kansas City, 2300 Holmes, Kansas City, MO 64108; telephone (816) 881-6150.

Stanford University Medical Center—1991: Updates in Ophthalmology

The Stanford University Medical Center course, 1991: Updates in Ophthalmology, will be held June 1, 1991. For additional information, write Continuing Education Programs, Dept. of Ophthalmology, A-157, Stanford Uni-

versity Medical Center, Stanford, CA 94305-5308; telephone (415) 725-7269.

Washington University School of Medicine: 31st Annual Spring Meeting

Washington University will hold its 31st Annual Spring Meeting and Eye Alumni Association Meeting, May 10 and 11, 1991. For further information, write Kathy Ryan, Washington University School of Medicine, Dept. of Ophthalmology, Box 8096, 660 S. Euclid Ave., St. Louis, MO 63110; telephone (314) 362-5722.

University of Washington: 17th Annual Resident Alumni Day Symposium

The University of Washington will sponsor its 17th Annual Resident Alumni Day Symposium, June 1, 1991, in Seattle, Washington. For further information, write Richard P. Mills, M.D., Dept. of Ophthalmology, University of Washington (RJ-10), Seattle, WA 98195; telephone (206) 543-3883.

American Society of Cataract and Refractive Surgery Executive Committee

The following are members of the American Society of Cataract and Refractive Surgery Executive Committee for 1991: president, Jack M. Dodick; president-elect, John D. Hunkeler; immediate past president, Guy E. Knolle, Jr.; secretary, Charles D. Kelman; chief financial officer, Spencer P. Thornton; program chairman, Manus C. Kraff; and ASCRS journal editor, Stephen A. Obstbaum.

(70)

MAY 15

1991

Acc 9 ⁷/₉₃

UCM

AMERICAN JOURNAL OF OPHTHALMOLOGY

Monthly since 1884

• ORIGINAL ARTICLES

Ocular Abnormalities in Premature Children

Gallo, Lennerstrand

Upshoot-Downshoot Phenomenon in Duane's Syndrome

Bloom, Graviss, Mardelli

Bilateral Congenital Oculomotor Nerve Palsy in a Child

Good, Barkovich, Nickel, Hoyt

Blind Spot Size and Optic Disk

Jonas, Gusek, Fernández

Oculomotor Nerve Palsy

Golnik, Miller

Squamous Cell Carcinoma of the Cornea

Cameron, Hidayat

Varicella Disciform Keratitis

Wilhelmus, Hamill, Jones

Visual Field in Diabetes With Glaucoma

Zeiter, Shin, Baek

Blood-Cell Velocity and Glaucoma

Gasser, Flammer

Comparison of Argon and Nd:YAG Iridotomy

Prum, Shields, Shields, Hickingbotham, Chandler

Scleral Buckling for Retinal Detachment

Rodriguez, Lewis, Kreiger, Yoshizumi, Sidikaro

Management of Ocular Toxoplasmosis

Engstrom, Holland, Nussenblatt, Jabs

Vitrectomy and Macular Hole

Mein, Flynn

Rhodopsin, Proline-347-Leucine

Berson, Rosner, Sandberg, Weigel-DiFranco, Dryja

Eyelash Nidus for Dacryoliths

Baratz, Bartley, Campbell, Garrity

Elastic Properties of the Lens Capsule

Assia, Apple, Tsai, Lim

Magnetic Resonance Imaging of Uveal Tumors

Raymond, Char, Norman, Protzko

• PERSPECTIVES

Assessment of Ophthalmic Training Programs

Broocker, Aaberg

• LETTERS TO THE JOURNAL

Capsulorhexis and pseudoexfoliation syndrome

Assia, Hoggatt, Apple

Administration of periocular corticosteroids

Joondeph

Tear cytology in conjunctival melanoma

Weiss, Perusse, Reale

Epiphora caused by blepharoptosis

Glatt

Ectropion and dipivefrin

Bartley

Contrast sensitivity and mountain sickness

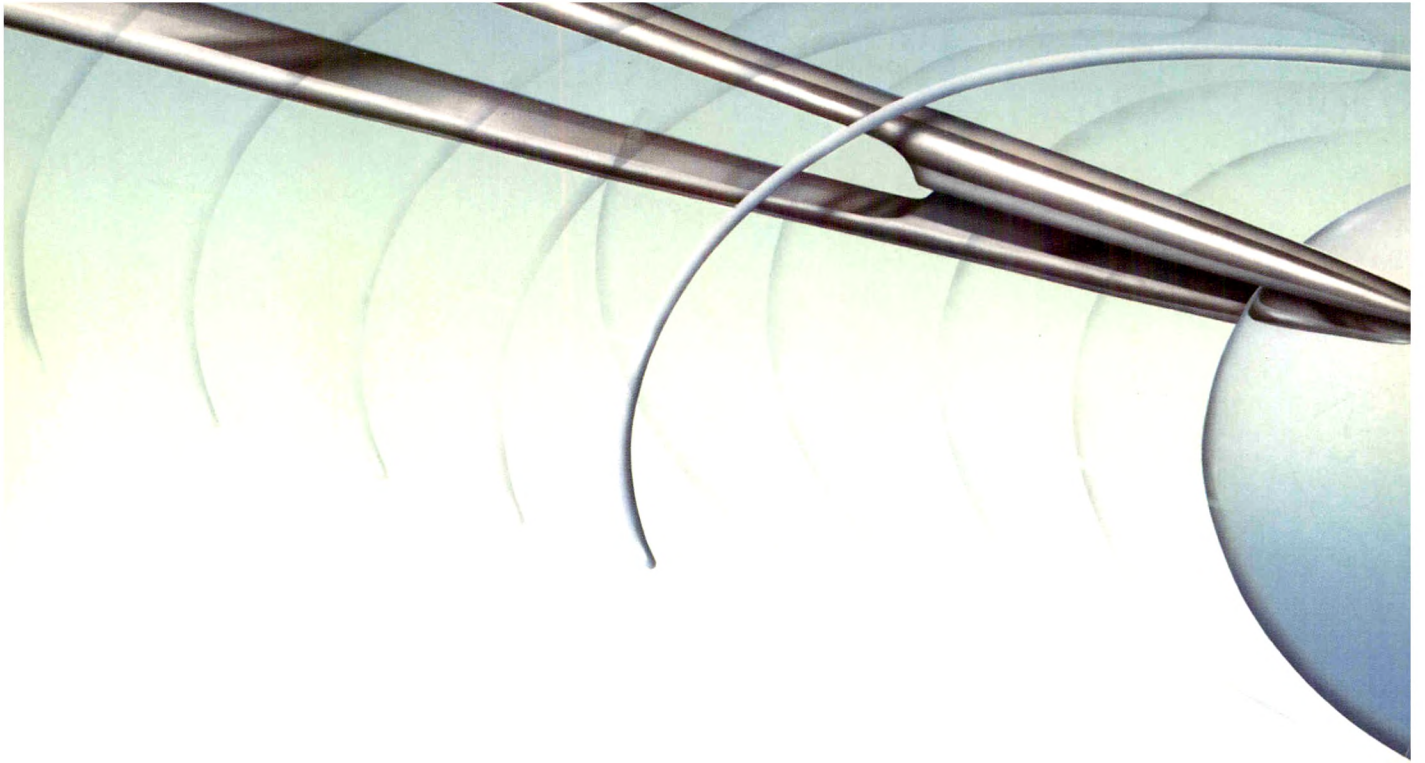
Nordmann, Roncin, Denis, Blein, Saraux

Endophthalmitis, diabetes, and renal papillary necrosis

Havunjian, Goldberg, Hepler

Clostridium perfringens endophthalmitis

Wiles, Ide



Viscoelastic
penetration
this dynamic is
the newest thing
you'll notice

Allergan Humphrey

Presents..

Ultimate Ultrasound

The New A/B Scan System 835

- Superb, high resolution images
- Digital scan storage to computer disk media
- Quad image mode allows serial scan comparison
- Easy-to-learn trackball control and on-screen icons guide operation
- Compact, lightweight, permanently sealed probes

*Quality, Performance and Innovation...
just what you expect from Humphrey.*



ALLERGAN HUMPHREY

© 1990 Allergan, Inc.

(800)-227-1508

(800)-826-6566 (In Calif.)

ORIGINAL ARTICLES

A population-based study of ocular abnormalities in premature children aged 5 to 10 years

Juan E. Gallo and Gunnar Lennerstrand 539

A magnetic resonance imaging study of the upshoot-downshoot phenomenon of Duane's retraction syndrome

Jeffrey N. Bloom, E. Richard Graviss, and Pierre G. Mardelli 548

Bilateral congenital oculomotor nerve palsy in a child with brain anomalies

William V. Good, A. James Barkovich, Bonnie L. Nickel, and Creig S. Hoyt 555

Correlation of the blind spot size to the area of the optic disk and parapapillary atrophy

Jost B. Jonas, Gabriele C. Gusek, and Martin C. Fernandez 559

Late recovery of function after oculomotor nerve palsy

Karl C. Golnik and Neil R. Miller 566

Squamous cell carcinoma of the cornea

James A. Cameron and Ahmed A. Hidayat 571

Varicella disciform stromal keratitis

Kirk R. Wilhelmus, M. Bowes Hamill, and Dan B. Jones 575

Visual field defects in diabetic patients with primary open-angle glaucoma

John H. Zeiter, Dong H. Shin, and Nam H. Baek 581

Blood-cell velocity in the nailfold capillaries of patients with normal-tension and high-tension glaucoma

Paul Gasser and Josef Flammer 585

In vitro videographic comparison of argon and Nd:YAG laser iridotomy

Bruce E. Prum, Jr., Steven R. Shields, M. Bruce Shields, Dyson Hickingbotham, and David B. Chandler 589

Scleral buckling for rhegmatogenous retinal detachment associated with severe myopia

Francisco J. Rodriguez, Hilel Lewis, Allan E. Kreiger, Marc O. Yoshizumi, and Yossi Sidikaro 595

Current practices in the management of ocular toxoplasmosis

Robert E. Engstrom, Jr., Gary N. Holland, Robert B. Nussenblatt, and Douglas A. Jabs 601

Recognition and removal of the posterior cortical vitreous during vitreoretinal surgery for impending macular hole

Calvin E. Mein and Harry W. Flynn, Jr. 611

Ocular findings in patients with autosomal dominant retinitis pigmentosa and rhodopsin, proline-347-leucine

Eliot L. Berson, Bernard Rosner, Michael A. Sandberg, Carol Weigel-DiFranco, and Thaddeus P. Dryja ... 614

An eyelash nidus for dacryoliths of the lacrimal excretory and secretory systems

Keith H. Baratz, George B. Bartley, R. Jean Campbell, and James A. Garrity 624

The elastic properties of the lens capsule in capsulorhexis

Ehud I. Assia, David J. Apple, Julie C. Tsai, and Edward S. Lim 628

Magnetic resonance imaging evaluation of uveal tumors

William R. Raymond IV, Devron H. Char, David Norman, and Eugene E. Protzko 633

PERSPECTIVES

Assessment of ophthalmic training programs

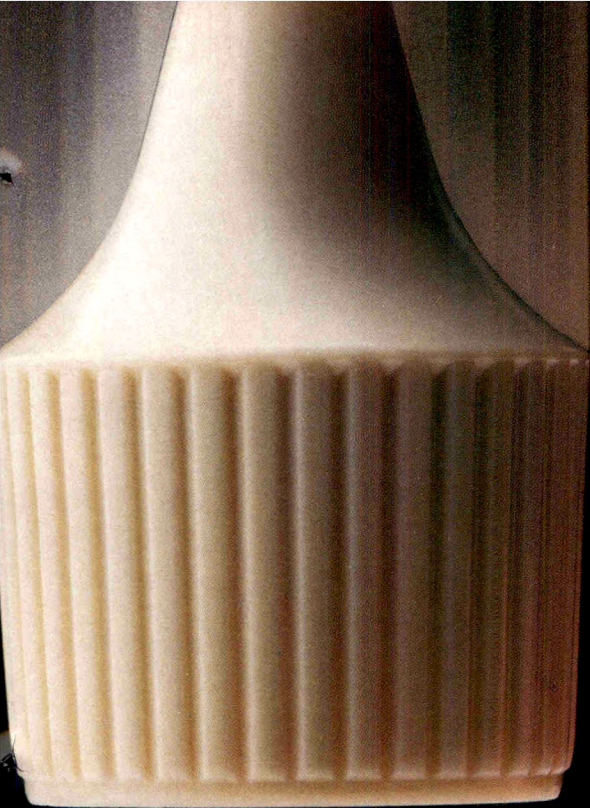
Geoffrey Broocker and Thomas M. Aaberg 642

LETTERS TO THE JOURNAL

Experimental nucleus extraction through a capsulorhexis in an eye with pseudoexfoliation syndrome. Ehud I. Assia, Judy P. Hoggatt, and David J. Apple, 645. A new technique for the administration of intraoperative periocular corticosteroids. Brian C. Joondeph, 647. Tear cytology in conjunctival melanoma. Jayne S. Weiss, Pascale Perusse, and Frank Reale, 648. Epiphora caused by blepharoptosis. Herbert J. Glatt, 649. Reversible lower eyelid ectropion associated with dipivefrin. George B. Bartley, 650. Contrast sensitivity as an early indicator of acute mountain sickness. Jean-Philippe Nordmann, Jean-Philippe Roncin, Philippe Denis, Jean-Pierre Blein, and Henry Saraux, 651. Bilateral endogenous endophthalmitis in a patient with diabetes and renal papillary necrosis. Richard H. Havunjian, Robert A. Goldberg, and Robert S. Hepler, 653. *Clostridium perfringens* endophthalmitis. Stephen B. Wiles and Carl H. Ide, 654.


CORRESPONDENCE

Delayed-onset pseudophakic endophthalmitis. Mark H. Haimann, Harold Weiss, and Joel A. Miller, 656. Reply. Gregory M. Fox, Brian C. Joondeph, Harry W. Flynn, Jr., Stephen C. Pflugfelder, and Thomas J. Roussel, 656. Increased intraocular pressure in severely burned patients. Russell W. Neuhaus, 657. Reply. Lawrence S. Evans, 658. Surgical management



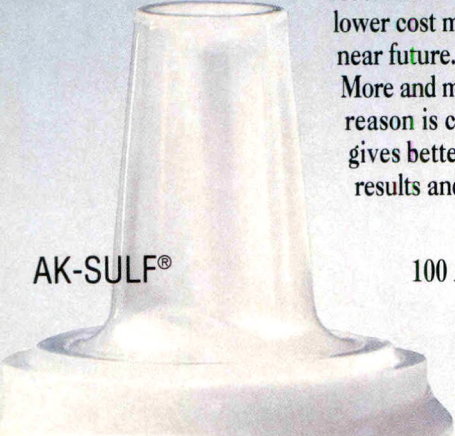
Akorn

**TOPS THEM ALL
WITH COMPLYING
COLORS**



When the American Academy of Ophthalmology requested pharmaceutical manufacturers to provide color-coded caps with all ophthalmic preparations, AKORN responded immediately. That's why AK-Sulf and AK-Pred are available with the tan and pink caps according to the AAO's recommendations. And the rest of AKORN's line of quality, lower cost medications will have color-coded caps in the very near future.

More and more physicians are prescribing AKORN, and the reason is clear. No other company responds faster and gives better service. AKORN... our products produce results and reduce costs. That's a promise.

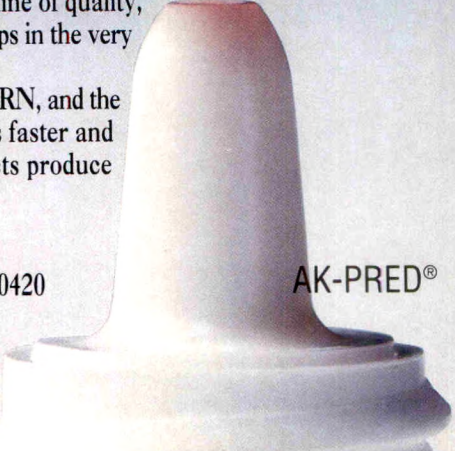


AK-SULF®

Akorn, Inc.
100 Akorn Drive, Abita Springs, LA 70420

1-800-535-7155
In Louisiana 1-800-344-2291
FAX 504-893-1257

NASDAQ Symbol: AKRN



AK-PRED®

TABLE OF CONTENTS (continued from Advertising page 6)

of oculomotor nerve palsy. Richard A. Saunders and Gary L. Rogers, 658. Reply. Irene Gottlob, Robert D. Reinecke, and Robert A. Catalano, 658.

BOOK REVIEWS

Orthoptic Assessment and Management (David Stidwill), 660. Wally, The Scholarly Walrus (Lee Hill), 660.

OBITUARY 661

ABSTRACTS 664

NEWS ITEMS 671

CLASSIFIEDS Begins on Advertising 41

COPYRIGHT TRANSFER Advertising 10

INSTRUCTIONS TO AUTHORS Advertising 33

PRODUCTS AND SERVICES Begins on Advertising 26

ADVERTISING INDEX Advertising 43

PUBLICATION STAFF

MARY L. BORYSEWICZ
Executive Managing Editor

LINDA G. CLAUSEN
Records Manager

KAREN D. JOHNSON
Manuscript Editor

MOLLY MELICK
Assistant to the Editor

DIANN J. MARQUIS
Editorial Assistant

MICHAEL J. LUND
Subscription Correspondent

LYNN ANN LINDVIG
AND
RENEE L. KASTAR
Sales and Production

Acc 9²/₉₃

A Population-Based Study of Ocular Abnormalities in Premature Children Aged 5 to 10 Years

Juan E. Gallo, M.D., and Gunnar Lennerstrand, M.D.

We studied the prevalence of ocular abnormalities in 528 children born prematurely (less than 1,501-g birth weight, less than 33 weeks' gestational age, or both) in Stockholm County from 1976 to 1981. The control group consisted of 1,047 randomly selected full-term children. Through various searches of the ophthalmic records from the period of 1981 to 1986 of Stockholm County, we found that 134 of the 528 premature children (25.4%) and 121 of the 1,047 full-term children (11.5%) had needed ophthalmic care for different reasons. The prevalence of ocular abnormalities was much higher in premature children than in full-term children: reduced visual acuity of 20/33 or worse in the best eye (21 of 528 [4.0%] and one of 1,047 [0.1%]); myopia (33 of 528 [6.3%] and 18 of 1,047 [1.8%]); anisometropia of 1 diopter or greater (31 of 528 [5.9%] and 15 of 1,047 [1.5%]); strabismus (52 of 528 [9.9%] and 22 of 1,047 [2.1%]); and nystagmus (13 of 528 [2.4%] and one of 1,047 [0.1%]). Children with birth weight less than 1,000 g had the highest rates of ocular abnormalities. We conclude that visual and oculomotor development of premature children should be carefully examined.

ADVANCES IN NEONATAL CARE during the last two decades have significantly increased the number of surviving children with low birth weights. Phelps¹ reported that the survival rate

of infants with a birth weight of less than 1,000 g increased from 8% in 1950 to approximately 35% in 1980. Thus, the population of infants with low birth weights, who are susceptible to retinopathy of prematurity, is considerably larger, and several studies have confirmed an increase in the incidence of retinopathy of prematurity.²⁻⁵ Important work has been done to clarify the natural progression of this disease^{3,6} as well as the role of retinopathy of prematurity in abnormal visual development, which results in ametropia and strabismus.⁷⁻¹⁰ Most investigators agree that the higher incidence of ocular problems in premature children than in full-term children is related to the occurrence of retinopathy of prematurity. The frequency of ocular changes, however, seems to vary between investigators, the area of survey, and the time of the study.¹¹⁻¹⁴ A detailed account of the incidence and nature of the ocular changes has been given by Fledelius¹⁵ for children born in Denmark during the years 1959 to 1961, but this was before the era of modern neonatology. Recently, Fledelius¹⁶ reported ocular conditions during the first years of life in children born between 1982 and 1987.

We determined the prevalence of ophthalmic anomalies in premature children compared with full-term children. The study was performed in a well-defined geographic area (Stockholm County) in children born between 1976 and 1981. The children were examined between 1981 and 1987 when they were 5 to 10 years of age. A preliminary report of some of the results has been published.¹⁷

Accepted for publication Jan. 28, 1991.

From the Department of Ophthalmology, Karolinska Institute, Huddinge University Hospital, Stockholm, Sweden. This study was supported by the Swedish Medical Research Council (grant 4751), Limmatt-Stiftung, KMA för synskadade, Stiftelsen Samariten, and Stiftelsen Sven Jerrings fond.

Reprint requests to Gunnar Lennerstrand, M.D., Department of Ophthalmology, Karolinska Institute, Huddinge University Hospital, S-14186 Huddinge, Sweden.

Patients and Methods

Epidemiologic data—All births in Sweden are reported to the Board of Health and Welfare. Among other things, the birth weight and the gestational age of the child are recorded together with information on the date of birth, the sex

of the child, and the like. The accuracy of the registration has been tested (report 1977-02-10 of the National Board of Health and Welfare). Deviations with regard to date of birth were found in 0.3%, to sex in 0.3%, and to weight in 1.0% of the reports. These numbers refer to the same period of time as our study.

The use of the ten-digit personal identification number in different Swedish registers makes it relatively easy to obtain information on the patients within the health care system and to monitor visits that the patients make to different hospitals and private offices. We used identification numbers obtained from the register at the Board of Health and Welfare in our search for visits of premature children and full-term children at the stations for neonatal care and ophthalmic care in the Stockholm County.

During the period of our investigation, all prematurely born children in Stockholm County were cared for at five different neonatal units. The treatment schemes of the departments were similar, at least for the same period of time, and advanced from an international standpoint.

Pediatric ophthalmology services are mainly provided at three departments in the Stockholm County. All children younger than the age of 5 years are referred to these centers with few exceptions. Older children were sometimes referred to a limited number of private ophthalmologists in Stockholm. With this knowledge of the system for pediatric ophthalmic care it was fairly easy to obtain complete information on the groups of children that we were interested in.

Between 1976 and 1981, premature children were not examined regularly by ophthalmologists in the neonatal wards, and there were no particular arrangements for subsequent ophthalmic examinations of these children. They were included in the general health care system for children, however, which implies that the child was examined regularly at the Health Care Centers for Children and referred for ophthalmic examination when needed. The children were screened for reduced visual acuity in each eye at the age of 3½ to 4 years and often also at 5 years. Those who were below the accepted limits of visual acuity were referred for ophthalmic examination. The limits were 20/30 at 4 years and 20/25 at 5 years. The rate of participation in these screening procedures has been between 95% and 98% of the population.¹⁸ As a result, few new cases of visual

impairment are discovered at visual acuity testing during first grade in school at 7 years of age when the screening at 3½ to 4 years is done correctly.^{19,20} At age 7 years monocular visual acuity should be 20/20. Most of the early ocular problems of children should therefore have been discovered and treated by the age of 5 years.

The system of health care for premature children and for full-term children in Stockholm County, with regard to pediatric and ophthalmic services, provides favorable opportunities for retrospective studies. The possibility of retrieving ophthalmic data for the population of preterm and full-term children obtained from the birth registers of the Board of Health and Welfare is good and probably hard to match elsewhere, except perhaps in the other Scandinavian countries.

Patient populations—From the birth registers of the Swedish National Board of Health and Welfare, all preterm children born in Stockholm County from Jan. 1, 1976, to Dec. 31, 1981, (a six-year period) were selected for the study if they had a birth weight less than 1,501 g, a gestational age less than 33 weeks, or both. Gestational age was determined according to the Dubowitz method.²¹ Our criteria for prematurity in this study included birth weight and gestational age since we wanted to reduce the number of children who had been described with an incorrect value in any of the variables. In recent studies, the most common single criterion has been birth weight of 1,500 g or less.²⁻⁵ The mean birth weight of Swedish premature children at 32 weeks' gestation, however, is 1,750 g. The limit of 1,500 g would have eliminated many premature children from our study. Nonetheless, premature children with a birth weight of 2,000 g or greater were excluded from the study.

The premature population consisted of 528 children, not including those who had died or moved from the area. The distribution with regard to birth weight and other details of the premature population is shown in Table 1. The control group of 1,047 children was also obtained from the birth registers of Stockholm County. It consisted of full-term children with a birth weight of 3,000 to 4,000 g and born on Jan. 15, March 15, May 15, July 15, Sept. 15, and Nov. 15 in the same period (1976 to 1981).

By means of listings of the ten-digit personal identification numbers of the two groups, searches were made directly at the departments of ophthalmology and other sources in Stock-

holm County as well as over the Stockholm County computer system. The investigation included patients who underwent ophthalmic care between 1981 and 1986 at the age of 5 to 10 years. One hundred thirty-four premature children and 121 full-term children had been seen by ophthalmologists and orthoptists for different reasons (Table 1). The charts of these children were analyzed with regard to several ophthalmic variables. The study was approved by the Ethical Committee of the Karolinska Institute, Stockholm, Sweden.

Ophthalmic examination—Every child underwent a standard examination of visual function and ocular motility. If the patient had been examined repeatedly, data from the most recent report were used.

Best-corrected visual acuity was determined with Snellen charts adapted to the age of the child. In the 5- to 6-year-old age group the lower limit of normal visual acuity was set at 20/25 and in the 7- to 10-year-old age group the lower limit was 20/20. Cycloplegic refraction was performed after topical instillation of atropine 1% (twice a day for 3½ days for a total of seven times) or a single instillation of a mixture of cyclopentolate hydrochloride 1% and phenylephrine hydrochloride 1.5%.²² As a measure of static refraction, the value was used with which the patient attained the best visual acuity. Spherical equivalents were calculated in patients with astigmatic refractive errors. Visual acuity was recorded in the better and the worse eye to evaluate the grade of visual handicap in each patient (Table 2). Amblyopia was considered to be present if there was a difference between the two eyes of more than two lines in visual acuity together with the presence

of strabismus or anisometropia. Blindness was defined as visual acuity of less than 20/600 in the better eye.

The ocular motility examination included determination of versions, near point of convergence, and cover/uncover tests at near and distance fixation. Some patients with phorias were also examined with dissociation tests: the Maddox cross at 5 meters and the Maddox wing test for near fixation.²³

Ocular deviations were determined with the prism cover test when the patient was wearing appropriate correction for refractive errors. Strabismus was defined as manifest or intermittent heterotropia, and in patients with a deviation of less than 10 prism diopters it was classified as microtropia. Fusion and stereopsis were tested with the Bagolini glasses and the Titmus test, respectively.

Results obtained at the last ophthalmic examination of each child were used. The age of each child was recorded in months from birth. The children were divided into three groups with regard to age for statistical purposes: 5 to 6 years, 7 to 8 years, and 9 to 10 years.

Prevalence was defined as the rate of known cases present in a defined population at a given time.²⁴ Comparisons between groups have been made with the chi-square test. P values less than .05 were considered significant.

Results

Ophthalmic care—The percentage of preterm children examined by ophthalmologists was

TABLE 1
DISTRIBUTION ACCORDING TO BIRTH WEIGHT OF PREMATURE AND FULL-TERM CHILDREN

	PREMATURE CHILDREN				FULL-TERM CHILDREN
	1,000 g	1,000–1,500 g	1,501–1,999 g*	TOTAL	3,000–4,000 g
No. of births	148	443	274	865	1,228
Survivors	48	311	242	601	1,224
Rate of survival	32.4%	70.2%	88.3%	69.5%	99.7%
No. moved away	5	37	31	73	177
No. available	43	274	211	528	1,047
No. of ophthalmic patients	19	79	36	134	121
Rate of ophthalmic care	44.1%	28.8%	17.0%	25.4%	11.5%

*Only patients younger than 33 weeks' gestational age.

TABLE 2
VISUAL ACUITY AND REFRACTIVE ERRORS

	PREMATURE CHILDREN (N = 528)	FULL-TERM CHILDREN (N = 1,047)
	NO. %	NO. %
Visual acuity		
Blind	2 (0.4)	—
≤20/66, worse eye	10 (1.9)	2 (0.2)
≤20/66, better eye	6 (1.1)	—
≤20/33, worse eye	38 (7.2)	6 (0.6)
≤20/33, better eye	21 (4.0)	1 (0.1)
Myopia	33 (6.3)	18 (1.8)
Unilateral	14 (2.7)	6 (0.6)
Bilateral	19 (3.6)	12 (1.2)
Anisometropia (diopters)	31 (5.9)	15 (1.5)
1-1.75 D	15 (2.8)	10 (1.0)
2-3.9 D	12 (2.3)	3 (0.3)
≥4 D	4 (0.8)	2 (0.2)

2.2 times higher than that of full-term children (Table 1). Referrals for ophthalmic examination were most common in the children with the lowest birth weights (less than 1,000 g).

Age at ophthalmic examination—The mean age of the preterm children was 84.9 months (standard deviation, ± 17.2) with a range of 60 to 131 months. The mean age of the full-term children was 92.4 months (standard deviation, ± 15.9) with a range of 62 to 131 months (Table 3).

The number of ophthalmic examinations in

age-specific groups of the premature population including the last examination were as follows: in the 5- to 6-year-old group, 533 examinations (mean, 7.5; standard deviation, 6.1); in the 7- to 8-year-old group, 361 examinations (mean, 8.2; standard deviation, 5.7); and in the 9- to 10-year-old group, 274 examinations (mean, 16.1; standard deviation, 14.2). The numbers included the examinations performed before the age of 5 years in the group of patients with extremely poor vision.

Visual acuity—Six preterm children had reduced visual acuity of 20/66 in the best eye, and two of these were blind as the result of retinopathy of prematurity (Table 2). In the remaining four children, retinopathy of prematurity was found in three patients and bilateral optic atrophy in one patient. Ten preterm children had a similar visual acuity in the worse eye. Two of the full-term children had visual acuity of 20/66 in one eye caused by either ocular trauma or anisometropic amblyopia because of high refractive error. Visual acuity of 20/33 in the better eye was found in 21 preterm children and in one full-term child. The difference between groups in occurrence of visual acuity reduction in the better eye was statistically significant (chi-square, 38.17; $P < .001$). Visual acuity of 20/33 in the worse eye was noted in 40 preterm and six full-term children. This difference was also statistically significant (chi-square, 60.3; $P < .001$).

Amblyopia—Organic or functional amblyopia was seen in 16 premature (3%) and three

TABLE 3
OCULAR ABNORMALITIES IN PREMATURE AND FULL-TERM CHILDREN ACCORDING TO AGE AT LAST EXAMINATION

	5-6 YEARS		7-8 YEARS		9-10 YEARS		TOTAL	
	PREMATURE (N = 69)	FULL TERM (N = 32)	PREMATURE (N = 46)	FULL TERM (N = 64)	PREMATURE (N = 19)	FULL TERM (N = 25)	PREMATURE (N = 134)	FULL TERM (N = 121)
	NO. %	NO. %	NO. %	NO. %	NO. %	NO. %	NO. %	NO. %
Visual acuity								
≤20/66, better eye	6 (8.7)	—	—	—	—	—	6 (4.5)	—
≤20/66, worse eye	6 (8.7)	—	2 (4.3)	1 (1.6)	2 (10.5)	1 (4)	10 (7.5)	2 (1.6)
≤20/33, better eye	14 (20.3)	—	6 (13)	1 (1.6)	1 (5.3)	—	21 (15.7)	1 (0.8)
≤20/33, worse eye	22 (31.9)	—	12 (26.1)	3 (4.7)	4 (21)	1 (4)	38 (28.3)	4 (3.3)
Anisometropia (diopters)								
1-1.75 D	8 (11.6)	1 (3.1)	6 (13)	4 (6.2)	1 (5.3)	5 (20)	15 (11.2)	10 (8.3)
2-3.9 D	9 (13)	—	1 (2.8)	3 (4.7)	2 (10.6)	—	12 (8.9)	3 (2.5)
≥4 D	1 (1.4)	—	3 (6.6)	—	—	2 (8)	4 (3)	2 (1.6)
Myopia (diopters)								
≤3D	11 (15.9)	4 (12.5)	7 (15.2)	10 (11)	3 (15.8)	3 (12)	21 (15.7)	17 (14)
>3D	6 (8.7)	—	4 (8.7)	1 (2.5)	2 (10.6)	—	12 (8.9)	1 (0.8)

full-term children (0.3%). The difference was statistically significant ($P < .001$). Among the possible causes of functional amblyopia in premature children, strabismus was found in 15 patients and anisometropia in eight. Causes for organic amblyopia were congenital glaucoma in one patient, vitreoretinal scarring caused by retinopathy of prematurity in four patients, and minimal signs of regressed retinopathy of prematurity (pigmentary changes, latticelike degeneration, and vitreoretinal interphase changes) in seven patients.

Refractive errors—A total of 33 of 528 (6.3%) preterm and 18 of 1,047 (1.8%) full-term children had myopic refractive errors (0.25 diopters or greater) in one or both eyes (Table 2). The difference between full-term children and premature children was statistically significant ($P < .001$). Myopia of greater than 3.00 diopters was seen in 12 (8.9%) premature children but only in one (0.8%) of the full-term children (Table 3).

The frequency of anisometropia, defined as a difference between eyes of 1 diopter or more in spherical equivalents, was higher in preterm (31 of 528 [5.9%]) than in full-term children (17 of 1,047 [1.6%]). This difference was also statistically significant ($P < .001$) (Table 2).

Ocular motility disorders—Strabismus was seen 4.7 times more often in preterm children than in full-term children ($P < .001$), with esotropia being the most common type in both groups (Table 4). Vertical deviations were often seen in addition to the horizontal strabismus. The time at which strabismus had started could not be evaluated in all cases. Binocular function measured with the Bagolini striated glasses was seen in some of the children with manifest strabismus, which explains why the number of patients with absence of binocularity was fewer than that with strabismus (Table 4).

Among preterm children, spontaneous nystagmus (horizontal and end-point) was seen more often than latent nystagmus (Table 4). Among full-term children only one case of latent nystagmus was observed, in a child with esotropia. The difference between preterm children and full-term children was statistically significant ($P < .001$).

Visual acuity and refractive errors in relation to age at follow-up examination—The percentage of premature children with visual acuity of 20/33 in the better eye was higher in the 5- to 6-year-old age group than in the other groups. However, six children with severe visual handicap (two blind, two with visual acuity of 20/

TABLE 4
OCULAR MOTILITY DISORDERS

	PREMATURE CHILDREN (N = 528)	FULL-TERM CHILDREN (N = 1,047)
	NO. %	NO. %
Strabismus	52 (9.9)	22 (2.1)
Esotropia	24 (4.6)	8 (0.9)
Exotropia	13 (2.5)	6 (0.6)
Microtropia*	15 (2.8)	7 (0.7)
Brown's syndrome	—	1 (0.1)
Nystagmus	13 (2.4)	1 (0.1)
Horizontal	6 (1.1)	—
End-point	2 (0.4)	—
Latent	5 (0.9)	1 (0.1)
Absence of binocularity	23 (4.3)	6 (0.6)

*Less than 10 diopters of deviation.

200, and two with visual acuity of 20/66), who had fundus anomalies were included in that group. Not taking into account these children in whom the age of examination could not be considered as a contributing factor, visual acuity of 20/33 in the better eye was seen in eight of 69 children (11.6%) and was similar to that found in the 7- to 8-year-old group. In the full-term group, no children in the 5- to 6-year-old age group had reduced visual acuity of this level. With respect to occurrence of mild and severe myopia, the distribution was the same in all age groups of preterm and full-term children, respectively.

Ocular findings in infants of very low birth weight—Ocular abnormalities were compared in groups of children with a birth weight of less than 1,000 g and 1,000 to 1,500 g (Table 5). The difference was statistically significant with regard to reduced visual acuity of 20/66, strabismus, and absence of binocularity.

Discussion

We found a much higher percentage of refractive errors, visual acuity reduction, and ocular motility disorders among the premature children than in the full-term children. The data on ocular changes were extracted from the records of pediatric ophthalmologists located in the area. The results seem unaffected by socioeconomic and geographic differences, insofar as the selection of the groups is concerned. It is

TABLE 5
OCULAR ABNORMALITIES IN PREMATURE CHILDREN
WITH BIRTH WEIGHT <1,000 G AND 1,000 TO 1,500 G

	<1,000 G (N = 43)	1,000-1,500 G (N = 274)	
	NO. %	NO. %	P VALUE
Visual acuity			
Blind	—	2 (0.7)	—
≤20/66, worse eye	4 (9.3)	5 (1.8)	<.025
≤20/66, better eye	3 (6.9)	1 (0.4)	<.005
≤20/33, worse eye	7 (16.3)	25 (9.1)	—
≤20/33, better eye	5 (11.6)	15 (5.5)	—
Myopia	5 (11.6)	22 (8.0)	—
Anisometropia	5 (11.6)	15 (5.5)	—
Strabismus	9 (20.9)	26 (9.5)	<.05
Nystagmus	4 (9.3)	9 (3.3)	—
Absence of binocularity	6 (13.9)	10 (3.6)	<.025

possible that socioeconomic factors were relevant for prematurity per se. Also the chances of not being able to monitor the children with respect to ophthalmic care would be the same in both groups.

We do not know to what extent ocular abnormalities would have been found in the groups of premature children and full-term children who did not have ophthalmic examinations. The risk of having missed patients with serious ocular aberrations, however, seems slight. Nevertheless, it is clear that incidence values of ocular abnormalities in children born prematurely in Stockholm between 1976 and 1981 cannot be reported, but we believe that the calculations of prevalence values are fairly correct.

The ophthalmic data in our study were obtained by different pediatric ophthalmologists in Stockholm when the children were between 5 and 10 years of age and were not the result of an examination by the same investigator at a specific age (about 10 years) as in the study by Fledelius.¹⁵ The programs for diagnosis and treatment of refractive errors and strabismus, however, were uniform at all the departments during the period of the study. Additionally, most of the children in the premature group were reexamined ophthalmoscopically by one of us (J.E.G.), and the results will be reported separately.

In populations of Danish children born prematurely or at full term, aged 8 to 11 years at the time of examination, Fledelius¹⁵ found bin-

ocular visual acuity (20/33 or worse) in 10.2% of the premature children and in 3.0% of the full-term children. We found lower rates of visual acuity changes in premature children (21 of 528 [4.0%]) and also lower values in the full-term group (one of 1,047 [0.1%]). This may reflect improved ophthalmic care for children during the period from the early 1960s, when the children in the study of Fledelius¹⁵ were born, to the end of the 1970s, the period of our study.

The rate of blindness in our study was low in comparison to the rate in other investigations (Table 6). Differences in prevalence values are probably because of improvements in neonatal care as well as selection of the population to be studied. Valentine and associates,²⁵ however, pointed out that the rate of blindness caused by retinopathy of prematurity may be increasing because of the increased survival of infants with low birth weight.²⁵

The high incidence of myopia detected in preterm children before they enter school is well known,^{26,27} and the role of retinopathy of prematurity in this anomaly has been reported.^{9,10,13,28} A direct comparison between children at school age, born prematurely, or at full term was carried out by Fledelius.¹⁵ He reported that 80 of 600 eyes (13.3%) in 300 premature children had myopic refractive errors and that 44 of 474 eyes (9.3%) in 237 control children had this refractive error. The findings of our study show a lower rate of myopia for both preterm and full-term children, and the difference between the two groups is larger. To some extent this may be because the children in our study were younger (5 to 10 years) than those in Fledelius's study (10 to 12 years), and that myopia detected at school ages is not as frequent in either group.

The rate of anisometropia in the premature group was about the same as in the study of Fledelius,¹⁵ but we cannot confirm the high incidence in full-term children reported there.

The prevalence of strabismus in the full-term population was similar to what was found previously in Sweden.²⁰ The frequencies of esotropia, microtropia, and exotropia had a similar pattern of distribution among preterm and full-term children, with esotropia being the most common type of strabismus in both groups, followed by microtropia and exotropia.

Fledelius¹⁵ reported an incidence of strabismus at 22.5% and 5.9%, respectively, in his study of premature and full-term children when they were 10 years of age (68 of 302

premature children and 14 of 237 control children). Our results show a lower rate, but the ratio between the two groups is similar. The study of Fledelius¹⁵ was performed on children born between 1959 and 1961, and it is possible that a more restrictive attitude toward applying oxygen therapy to neonates prevailed at that time.^{15,28,29} This might have increased the risk for hypoxic brain lesions in the premature children³⁰ and subsequently the incidence of strabismus, which is known to be high in children with general brain damage.³¹ However, the prevalence of strabismus in full-term children was also high in the study of Fledelius,¹⁵ and this cannot be explained in the same way. An Australian survey¹³ showed that 19% of the preterm children were affected with strabismus. This study was carried out in one single hospital, which can lead to higher values compared with studies carried out on the population in a specific area. Reports from other populations show prevalence values of strabismus similar to ours.^{32,33}

Kushner⁷ reported a higher incidence of strabismus in premature children with and without retinopathy of prematurity (13 of 38 [34%] and five of 38 [13%]) than in full-term children (one of 38 [2.5%]). We did not evaluate the occurrence of acute retinopathy of prematurity since no examination of the preterm children had been performed regularly in the neonatal period. Information on late fundus changes, however, available from a follow-up examination of the premature children confirmed Kushner's findings. From these results it seems reasonable to assume that prematurity per se and its influence on brain development can affect the normal development of ocular motility and binocular functions. How this occurs is unclear. It is known that premature infants are more susceptible to intracerebral hemorrhages,³⁴ which could be a contributing factor in the development of strabismus.³⁵ There are several other factors during the neonatal period that can affect the function of the central nervous system and, as a consequence, induce ocular motility disorders. Among those are hypoxia,³⁶ kernicterus (hyperbilirubinemia),³⁷ oxygen therapy in excess,³⁸ and possibly hypernatremia, which may produce edema of the brain.³⁶

The most important factor for the differences between our results and those of other researchers is probably that previous studies were not population based and had other criteria for selection of patient and control groups than

ours. Studies on a population within a specific geographic area are likely to give lower prevalence values than those obtained at centers with a referral-based population (Table 6).^{5,12,16,39-41}

All variables analyzed in this study (visual acuity, amblyopia, myopia, anisometropia, strabismus, nystagmus, absence of binocularity) disclosed a higher prevalence of ocular disturbances in preterm than in full-term children. The age at which the children were last examined and at which the ophthalmic data were recorded was about six months higher in full-term children than in preterm children. The difference probably reflects variations in referral criteria between the preterm and full-term children, in that suspected eye-related problems in full-term children are more prone to appear during school years. In preterm children, ocular abnormalities are more often detected earlier at the visual screening at 3½ to 4 years of age or at other visits to the health care centers for preschool children. Age at examination, however, did not account for the differences between groups with regard to visual acuity reduction, since these visual acuity levels were set below the age norm even for the youngest children examined, and there were no 5- to 6-year-old full-term children who had reduced visual acuity. The occurrence of mild myopia was equally distributed between age groups in

TABLE 6
PREVALENCE OF BLINDNESS CAUSED BY
RETINOPATHY OF PREMATURITY

STUDY	YEARS	CRITERIA*	NO. AT RISK	RATE OF BLINDNESS
Alberman, Benson, and Evans ¹²	1970, 1971-1973	I	347	1.4%
Gunn and associates ³⁹	1975-1976	I	80	2.5%
Fledelius ¹⁶	1982-1987	I	124	4%
Kalina and Karr ⁴⁰	1960-1980	I	1,051	0.5%
Phelps ⁴¹	—	I	—	1.8%-4%
Darlow ⁵	1986	I	337	2%
Present study	1976-1981	II	528	0.4%
Present study	1976-1981	I	317	0.6%

*I indicates birth weight of less than 1,500 g; II indicates birth weight of less than 1,501 g, gestational age of younger than 33 weeks, or both.

preterm and normal children, respectively. This means that differences in prevalence of myopia that were found would not be influenced by age factors. The number of referrals of children to ophthalmologists from preschool health care centers (up to the age of 7 years) and schools (from the age of 7 years) is high also in the full-term group. In addition to documented or suspected reduced vision and binocular problems, the full-term children were referred for reading difficulties, headache, and other presumed visual and oculomotor problems. This would explain why relatively few full-term children were found to have ocular abnormalities and refractive errors.

Phelps⁴¹ reported that premature children with a birth weight below 1,000 g had the highest rate of ophthalmic problems. There are clear differences also between the children with birth weight of 1,000 to 1,500 g and the full-term children. This implies that premature children constitute a definite risk group not only with regard to ocular disease during the acute phase of prematurity but also with regard to later ocular complications and deviations in visual development.

ACKNOWLEDGMENT

Anders Eriksson, of the Swedish National Board of Health and Welfare, obtained data from the birth registers.

References

1. Phelps, D. L.: Vision loss due to retinopathy of prematurity. *Lancet* 606:1, 1981.
2. Campbell, P., Bull, M., Ellis, F., Bryson, C., Lemons, J., and Schreiner, R.: Incidence of retinopathy of prematurity in a tertiary newborn intensive care unit. *Arch. Ophthalmol.* 101:1686, 1983.
3. Flynn, J., Bancalari, E., Bachynski, B., Buckley, E., Bawol, R., Goldberg, R., Cassady, J., Schiffman, J., Feuer, W., Gillings, D., Sim, E., and Roberts, J.: Retinopathy of prematurity. Diagnosis, severity, and natural history. *Ophthalmology* 94:620, 1987.
4. Schulenburg, W. E., Prendiville, A., and Ohri, R.: Natural history of retinopathy of prematurity. *Br. J. Ophthalmol.* 71:837, 1987.
5. Darlow, B. A.: Incidence of retinopathy of prematurity in New Zealand. *Arch. Dis. Child.* 63:1083, 1988.
6. Tasman, W.: The natural history of active retinopathy of prematurity. *Ophthalmology* 91:1499, 1984.
7. Kushner, B. J.: Strabismus and amblyopia associated with regressed retinopathy of prematurity. *Arch. Ophthalmol.* 100:256, 1982.
8. Schaffer, D. B., Quinn, G. E., and Johnson, L.: Sequelae of arrested mild retinopathy of prematurity. *Arch. Ophthalmol.* 102:373, 1984.
9. Nissenkorn, I., Yassur, Y., Mashkowski, D., Sherf, I., and Ben-Sira, I.: Myopia in premature babies with and without retinopathy of prematurity. *Br. J. Ophthalmol.* 67:170, 1983.
10. Gordon, R. A., and Donzis, P. B.: Myopia associated with retinopathy of prematurity. *Ophthalmology* 93:1593, 1986.
11. Zacharias, L., Chisholm, J. F., Jr., and Chapman, R. B.: Visual and ocular damage in retrolental fibroplasia. *Am. J. Ophthalmol.* 53:337, 1962.
12. Alberman, E., Benson, J., and Evans, S.: Visual defects in children of low birthweight. *Arch. Dis. Child.* 57:818, 1982.
13. Keith, C. G., and Kitchen, W. H.: Ocular morbidity in infants of very low birth weight. *Br. J. Ophthalmol.* 67:302, 1983.
14. Hammer, H. M., Noble, B. A., Harcourt, R. B., and Congdon, P. J.: Ophthalmic findings in very low birth weight children. *Trans. Ophthalmol. Soc. U.K.* 104:329, 1985.
15. Fledelius, H.: Prematurity and the eye. *Acta Ophthalmol.* 128:3, 1976.
16. ———: Retinopathy of prematurity. Clinical findings in a Danish county 1982–87. *Acta Ophthalmol.* 68:209, 1990.
17. Lennerstrand, G., and Gallo, J. E.: Prevalence of refractive errors and ocular motility disorders in 5–10 years old Swedish children born prematurely or at full-term. *Acta Ophthalmol.* 67:717, 1989.
18. National Board of Health and Welfare: Public health in Sweden 1978. Official statistics of Sweden. Stockholm, Liber Förlag, 1981.
19. Köhler, L., and Stigmar, G.: Vision screening of four-year-old children. *Acta Paediatr. Scand.* 62:17, 1973.
20. ———: Visual disorders in 7-year-old children with and without previous vision screening. *Acta Paediatr. Scand.* 67:373, 1978.
21. Dubowitz, L., Dubowitz, V., and Goldberg, C.: Clinical assessment of gestational age in the newborn infant. *J. Pediatr.* 77:1, 1970.
22. Zetterström, C.: A cross-over study of the cycloplegic effects of a single topical application of cyclopentolate-phenylephrine and routine atropinization for 3.5 days. *Acta Ophthalmol.* 63:525, 1985.
23. Duke-Elder, S.: Anomalies of the ocular movements. In Duke-Elder, S. (ed.): *The Neurology of Vision Motor and Optical Anomalies. Textbook of Ophthalmology*, vol 4. London, Henry Kimpton, 1949, pp. 3881–3882.
24. Alberman, E. D.: Epidemiology of retinopathy of prematurity. In Sylverman, W., and Flynn, J. (eds.): *Retinopathy of Prematurity*. Boston, Blackwell Scientific Publications, 1985, pp. 249–266.

25. Valentine, P., Jackson, C., Kalina, R., and Woodrum, D.: Increased survival of low birth weight infants. Impact on the incidence of retinopathy of prematurity. *Pediatrics* 84:442, 1989.
26. Drillien, C. M.: Growth and development in a group of children of very low birth weight. *Arch. Dis. Child.* 33:10, 1958.
27. Dobson, V., Fulton, A. B., Manning, K., Salem, D., and Petersen, R. A.: Cycloplegic refractions of premature infants. *Am. J. Ophthalmol.* 91:490, 1981.
28. Tasman, W.: Late complications of retrolental fibroplasia. *Ophthalmology* 86:1724, 1979.
29. Patz, A., and Payne, J.: Retinopathy of prematurity (retrolental fibroplasia). In Tasman, W., and Jaeger, E. A. (eds.): *Duane's Clinical Ophthalmology*, vol. 3, chap. 20. Philadelphia, J. B. Lippincott, 1989, pp. 1-19.
30. McDonald, A.: Cerebral palsy in children of very low birth weight. *Arch. Dis. Child.* 38:579, 1963.
31. Lennerstrand, G.: Motor dysfunction in strabismus. In Lennerstrand, G., von Noorden, G. K., and Campos, E. C. (eds.): *Strabismus and Amblyopia*. Wenner-Gren International Symposium Series, 1988, pp. 5-22.
32. Frandsen, A.: Occurrence of squint. *Acta Ophthalmol.* 62, 1960.
33. Graham, P. A.: Epidemiology of strabismus. *Br. J. Ophthalmol.* 58:224, 1974.
34. Walsh, F., and Hoyt, W.: *Clinical Neuro-Ophthalmology*, ed. 3, vol. 3. Baltimore, Williams & Wilkins, 1969, pp. 2334-2337.
35. Tamura, E. E., and Hoyt, C. S.: Oculomotor consequences of intraventricular hemorrhages in premature infants. *Arch. Ophthalmol.* 105:533, 1987.
36. Walsh, F., and Hoyt, W.: *Clinical Neuro-Ophthalmology*, ed. 3, vol. 1. Baltimore, Williams & Wilkins, 1969, pp. 860-862.
37. Walsh, F., and Hoyt, W.: *Clinical Neuro-Ophthalmology*, ed. 3, vol. 2. Baltimore, Williams & Wilkins, 1969, p. 1034.
38. Haugaard, N.: Cellular mechanism of oxygen toxicity. *Physiol. Rev.* 48:352, 1968.
39. Gunn, T. R., Easdown, J., Outerbridge, E. W., and Aranda, J. V.: Risk factors in retrolental fibroplasia. *Pediatrics* 65:1096, 1980.
40. Kalina, R. E., and Karr, D. J.: Retrolental fibroplasia. Experience over two decades in one institution. *Ophthalmology* 89:91, 1982.
41. Phelps, D. L.: Retinopathy of prematurity. An estimate of vision loss in the United States, 1979. *Pediatrics* 67:924, 1981.

A Magnetic Resonance Imaging Study of the Upshoot-Downshoot Phenomenon of Duane's Retraction Syndrome

Jeffrey N. Bloom, M.D., E. Richard Graviss, M.D., and Pierre G. Mardelli, B.S.

Patients with Duane's retraction syndrome may have an associated upshoot or downshoot of the involved eye in adduction. This vertical movement has been attributed to the lateral rectus muscle slipping over or under the globe and acting as an elevator or depressor, respectively ("bridle-effect"). We used magnetic resonance imaging to investigate this phenomenon in two patients, one with an overshoot and the other with an undershoot. Minimal vertical displacement of the lateral rectus muscle in relation to the orbit was noted both on upshoot and downshoot. The bridle-effect theory must be modified to account for this finding.

DUANE'S RETRACTION SYNDROME is a congenital disorder of ocular motility characterized by an anomalous innervation of the lateral rectus muscle of the affected eye. It may be divided into three types based upon clinical and electromyographic findings.¹ Type I is the most frequent. Patients with this subtype have a marked limitation of abduction, with normal or slightly decreased adduction. Type II is characterized by diminished adduction and normal or mildly limited abduction. Patients with Type III

have both poor adduction and abduction of the affected eye. Each of these subgroups of Duane's retraction syndrome manifest a globe retraction on attempted adduction, produced by the cocontraction of the medial and lateral recti muscles of the involved eye.²

An upshoot or downshoot of the affected eye as it adducts has been noted in some patients of all three Duane's retraction syndrome categories.³⁻⁵ It has been suggested that this abnormality is the result of a "bridle" or "leash" phenomenon produced by a tight lateral rectus muscle that slips over or under the globe and produces an anomalous vertical movement of the eye.^{2,6,7} Various surgical procedures based upon this theory have been designed to correct this disfiguring complication of Duane's retraction syndrome.^{3,7,8}

To understand better the upshoot-downshoot phenomenon, we used magnetic resonance imaging to examine the relative positions of the horizontal recti muscles and the globes of two patients with Duane's retraction syndrome with these abnormalities.

Patients and Methods

Case 1

A 25-year-old man with visual acuity of 20/20 in each eye was orthophoric in primary gaze (Fig. 1). The left eye, however, could be abducted only 5 degrees past the midline. A widening of the palpebral fissure of this eye was noted on attempted abduction, whereas a narrowing of the fissure and retraction of the globe occurred with attempted adduction. Additionally, a marked upshoot of the left eye was noted on attempted adduction. Duane's retraction syndrome Type III was diagnosed.¹ An incidental finding was long-standing blepharoptosis and miosis of the non-Duane's retraction syndrome

Accepted for publication Jan. 21, 1991.

From the Departments of Ophthalmology (Dr. Bloom) and Diagnostic Imaging (Dr. Graviss), Cardinal Glennon Children's Hospital, St. Louis, Missouri; and Department of Ophthalmology (Dr. Bloom and Mr. Mardelli), Bethesda Eye Institute, St. Louis University School of Medicine, St. Louis, Missouri. This study was supported in part by an unrestricted grant from Research to Prevent Blindness, Inc. This study was presented as a poster at the Association for Research in Vision and Ophthalmology Annual Meeting, May 3, 1991, Sarasota, Florida.

Reprint requests to Jeffrey N. Bloom, M.D., Bethesda Eye Institute, St. Louis University School of Medicine, 3655 Vista Ave., St. Louis, MO 63110.

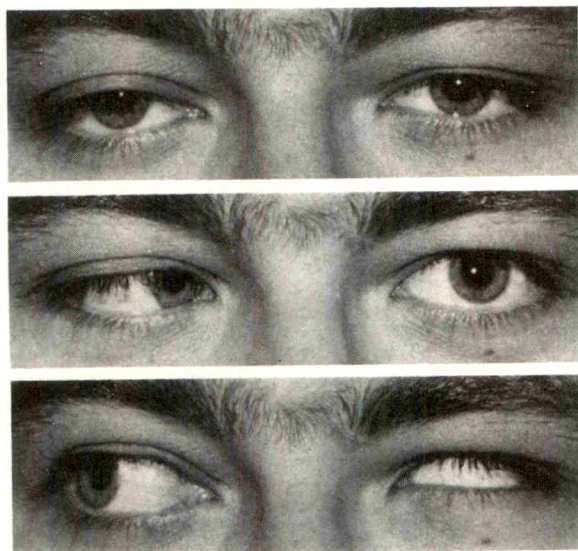


Fig. 1 (Bloom, Graviss, and Mardelli). Case 1. Top, Patient is orthophoric in primary gaze. Middle, On left gaze, the left eye can abduct only approximately 5 degrees. There is an associated widening of the palpebral fissure of this eye. Bottom, On attempted adduction, there is a narrowing of the eyelid fissure, retraction of the globe, and an upshoot of the eye.

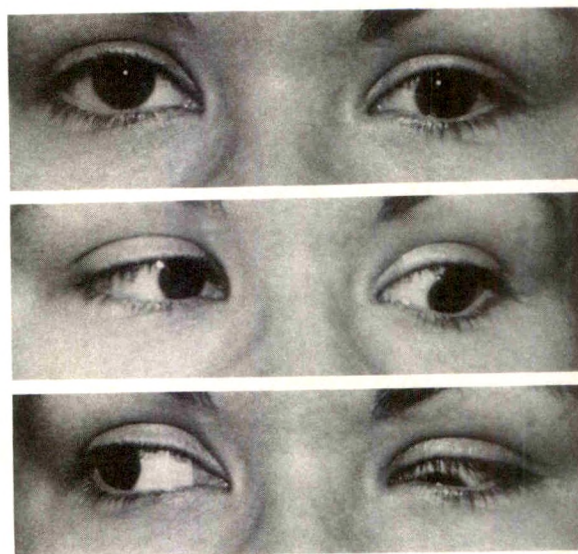


Fig. 2 (Bloom, Graviss, and Mardelli). Case 2. Top, Patient has a left exotropia of 15 prism diopters and a left hypotropia of 5 prism diopters in primary gaze. Middle, Mild limitation of abduction of the left eye is noted in left gaze. Bottom, Downshoot of the left eye occurs on attempted adduction. The limited adduction is accompanied by globe retraction and eyelid fissure narrowing.

right eye, which suggested a possible congenital Horner's syndrome. Heterochromia was difficult to assess because of the light color of the irides. No other neurologic abnormalities were noted.

Case 2

A 34-year-old woman with visual acuity of 20/20 in each eye had a left exotropia of 15 prism diopters and a left hypotropia of 5 prism diopters in primary gaze (Fig. 2). A 5-degree head turn to the right was also noted. There was mild limitation of abduction of the left eye. Marked limitation of adduction of this eye, in association with globe retraction and eyelid fissure narrowing, was observed. A downshoot of the left eye accompanied adduction. Duane's retraction syndrome Type II was diagnosed.¹

Each patient was scanned on a 0.4-T magnetic resonance imager, using a quadrature head coil to evaluate the orbit. T₁-weighted images were obtained with scanning sequences maximized for image quality and short scanning times. The orbit was localized with an axial scan, followed by a series of off-axis coronal scans aligned perpendicular to the central axis of the orbit. Serial 5-mm contiguous images

were obtained for each eye in primary gaze, as well as horizontal and vertical gazes. The natural contrast between the globe, extraocular muscles, and retrobulbar fat allowed for direct visualization of the extraocular muscles. Written consent was obtained from each patient before this study.

Results

To visualize the relative movements of the muscles, line drawings were made from the scans in primary gaze for each eye, adduction for the abnormal eye, and either upgaze or downgaze for the fellow normal eye. Magnetic resonance images were obtained for each eye at corresponding positions through the globe and through the retrobulbar muscle cone. Anterior sections were selected as close as possible to the point of tangency of the horizontal recti muscles on the eye in order to visualize the muscle movement over the surface of the globe.⁹ Superimpositions of the drawings for primary gaze and for adduction of the affected eye were constructed, as well as superimpositions of primary gaze and vertical gaze of the

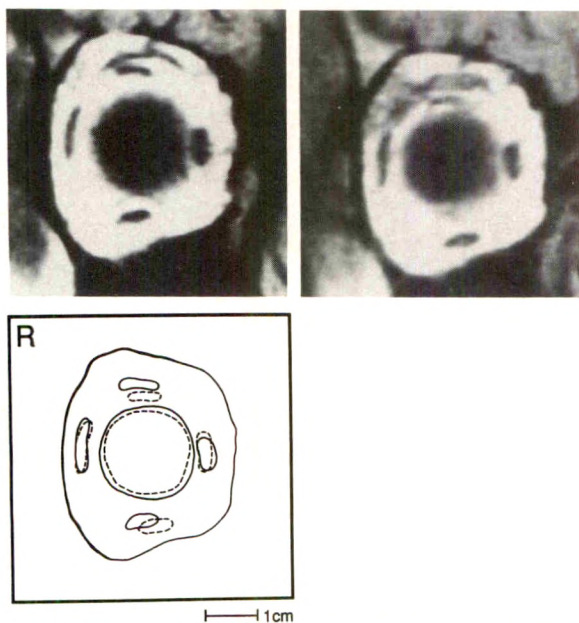


Fig. 3 (Bloom, Graviss, and Mardelli). Case 1. Top left, Coronal image through the normal right eye in primary gaze. Top right, Same eye in upgaze. Bottom left, Superimposition of primary gaze (solid line) and upgaze (dotted line).

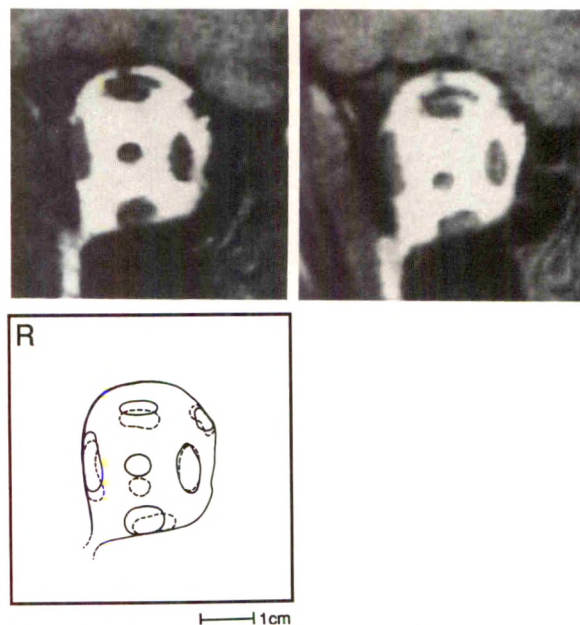


Fig. 4 (Bloom, Graviss, and Mardelli). Case 1. Top left, Coronal image through the muscle cone of the normal right eye in primary gaze. Top right, Same eye in upgaze. Bottom left, Superimposition of primary gaze (solid line) and upgaze (dotted line).

unaffected eye, to evaluate the displacement of the muscles after movement of the globe. A similar method was used by Simonsz and associates.¹⁰

The most obvious indication on a magnetic resonance image scan of a vertical displacement in the gaze position of an eye is the change in the position of the optic nerve.¹¹ The nerve moves in a vertical direction opposite to that of the globe. For the patient in Case 1 (Figs. 3 through 6), a downward shift of the optic nerve was noted in the scans of upgaze of the normal eye (Fig. 4) and upshoot on adduction of the abnormal eye (Fig. 6). In neither eye, however, was there more than a 1- to 2-mm displacement in the vertical position of the lateral recti muscles. The findings in Case 2 demonstrate the expected upward shift of the optic nerve on downward movement in each eye, but no measurable change in the position of the lateral rectus muscle of the normal eye, and only approximately 1 mm of vertical displacement of this muscle in the abnormal eye (Figs. 7 through 10). In neither patient did the lateral rectus muscle, relative to the fixed position of the orbit, move over the top or under the bottom of the affected globe.

Discussion

The explanation for the upshoot-downshoot phenomenon of Duane's retraction syndrome is unsettled and controversial. Duane¹² attributed it to the "spasmodic action of the inferior or superior oblique, probably often combined with spasm of the superior or inferior rectus." Currently, the proposed origins for these anomalous vertical movements are usually classified as either innervational or mechanical.

An electromyographic study by Scott and Wong¹³ demonstrated that elevation in adduction was accompanied by innervation activity of the superior rectus muscle, with or without simultaneous inferior oblique muscle activity. They cited a written communication describing a patient in whom a free tenotomy of the superior rectus muscle and a counterbalancing free tenotomy of the inferior rectus muscle reduced both the elevation on adduction and the retraction of the affected globe. Parks and Eisenbaum³ and Kraft² used vertical muscle surgery to treat the upshoot, but in all cases the procedures were combined with either a recession or posterior fixation suture of the lateral

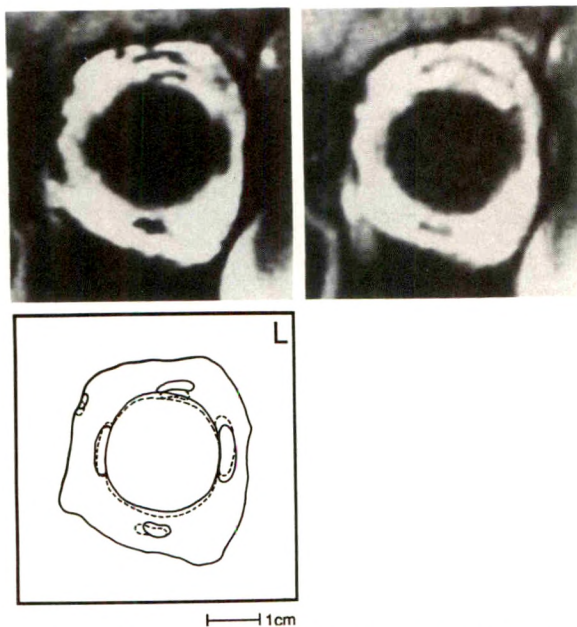


Fig. 5 (Bloom, Graviss, and Mardelli). Case 1. Top left, Coronal image through the abnormal left eye in primary gaze. Top right, Same eye in upshoot on attempted adduction. Bottom left, Superimposition of primary gaze (solid line) and upshoot (dotted line).

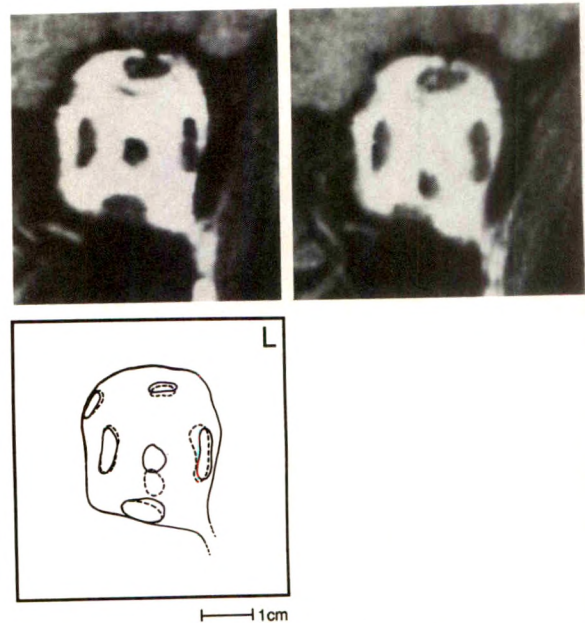


Fig. 6 (Bloom, Graviss, and Mardelli). Case 1. Top left, Coronal image through the muscle cone of the abnormal left eye in primary gaze. Top right, Same eye in upshoot. Bottom left, Superimposition of primary gaze (solid line) and upshoot (dotted line).

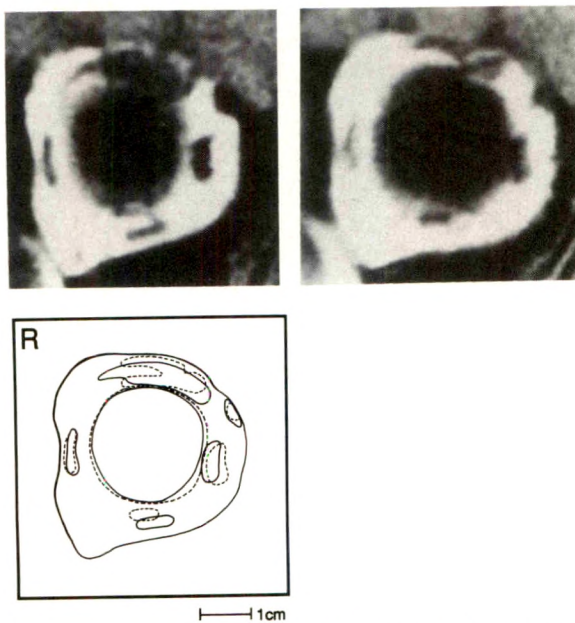


Fig. 7 (Bloom, Graviss, and Mardelli). Case 2. Top left, Coronal image through the normal right eye in primary gaze. Top right, Same eye in downgaze. Bottom left, Superimposition of primary gaze (solid line) and downgaze (dotted line).

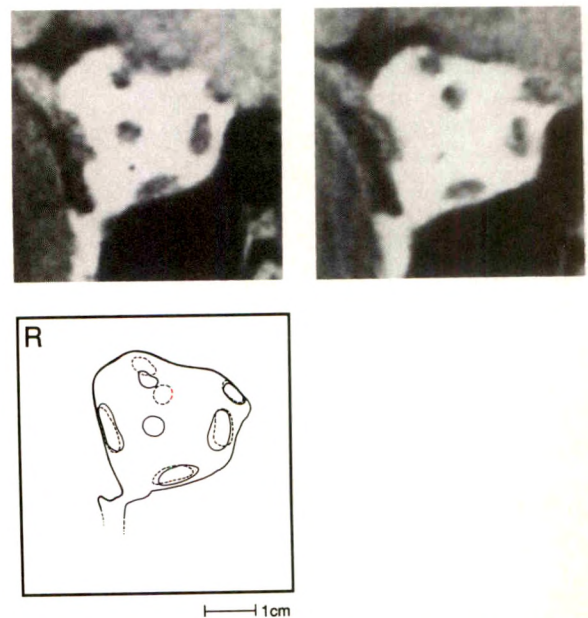


Fig. 8 (Bloom, Graviss, and Mardelli). Case 2. Top left, Coronal image through the muscle cone of the normal right eye in primary gaze. Top right, Same eye in downgaze. Bottom left, Superimposition of primary gaze (solid line) and downgaze (dotted line).

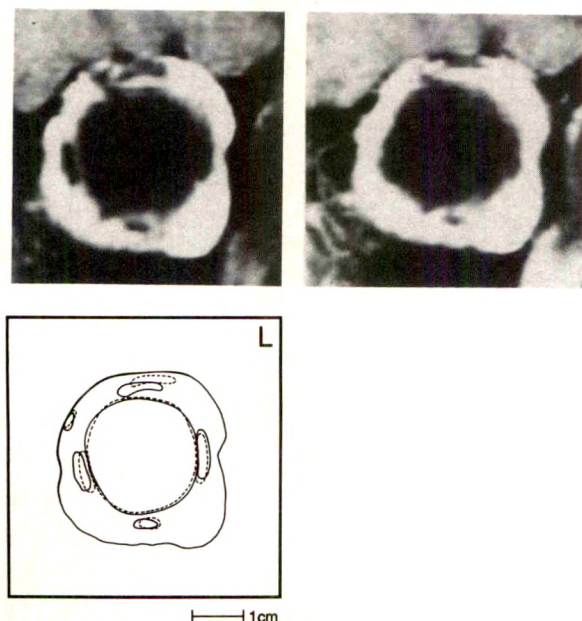


Fig. 9 (Bloom, Graviss, and Mardelli). Case 2. Top left, Coronal image through the abnormal left eye in primary gaze. Top right, Same eye in downshoot. Bottom left, Superimposition of primary gaze (solid line) and downshoot (dotted line).

rectus muscle. Von Noorden and Murray¹⁴ reported an inability to improve the upshoot-downshoot movements with inferior or superior oblique muscle weakening procedures, combined with or followed by posterior fixation of the superior rectus muscle.

The mechanical theory of the upshoot-downshoot phenomenon attributes these movements to a tight lateral rectus muscle that slips over or under the globe and acts as an elevator or depressor of the eye.^{6,15,16} This "bridle" or "leash" effect is produced by the cocontraction of the horizontal recti muscles on attempted adduction. Magoon and associates¹⁷ demonstrated the involvement of the lateral rectus muscle by reducing the overshoot of a patient with Duane's retraction syndrome after the injection of this muscle with lidocaine. Jampolsky¹⁸ reported the elimination of the overshoot of a patient with Duane's retraction syndrome by the detachment of the lateral rectus muscle, under topical anesthesia. Several different surgical techniques predicated upon the bridle effect theory have been used to treat the upshoot-downshoot abnormality. These procedures include the following: recession of the medial and lateral recti muscles to the equator of the globe^{15,16}; posterior fixation of both hori-

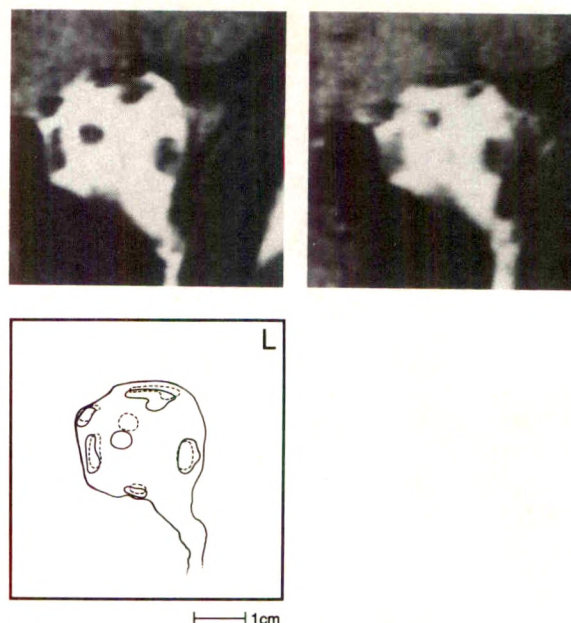


Fig. 10 (Bloom, Graviss, and Mardelli). Case 2. Top left, Coronal image through the muscle cone of the abnormal left eye in primary gaze. Top right, Same eye in downshoot. Bottom left, Superimposition of primary gaze (solid line) and downshoot (dotted line).

zontal recti muscles^{14,16} or of the lateral rectus muscle alone⁸; and a splitting of the lateral rectus muscle, with or without a recession, into a Y-shaped configuration to stabilize the muscle's position on the globe.^{7,8}

Discussions of the bridle-effect theory have suggested that the lateral rectus muscle is mobile and that it slips vertically across the globe to produce an upshoot or downshoot.^{5,7,8,16} Studies of normal subjects using computed tomography¹⁰ and magnetic resonance imaging,¹¹ however, demonstrated no vertical displacement of the horizontal recti muscles, relative to the orbit, on upgaze and downgaze. Our study was undertaken to determine whether the lateral rectus muscle of a patient with Duane's retraction syndrome with an upshoot or downshoot would shift vertically, relative to the orbit, as the eye elevated or depressed in adduction.

Our results indicate that there is minimal vertical movement of the lateral rectus muscle, in relation to the orbit, as the eye either upshoots or downshoots in adduction. This finding was previously postulated by von Noorden and Murray,¹⁴ based upon the computed tomography and magnetic resonance imaging studies

of Simonsz and associates¹⁰ and Miller,¹¹ respectively. It is not the purpose of our investigation to prove or disprove the bridle-effect theory. The findings of several reports^{3,6-8,14-18} suggest that the lateral rectus muscle contributes to the upshoot-downshoot abnormality of the Duane's retraction syndrome, as predicted by this model. Our findings indicate, however, that the bridle-effect theory must be modified to account for the minimal vertical displacement of the lateral rectus muscle on both upshoot and downshoot.

A recent study by Miller, Demer, and Rosenbaum¹⁹ also used magnetic resonance imaging to examine a patient with Duane's retraction syndrome (Type I) with an upshoot and another patient (bilateral Type I) with a downshoot. No vertical displacement of the lateral rectus muscle was noted on upshoot, whereas a 1- to 2-mm displacement was detected on downshoot. These findings are similar to those of our patients, although not identical for the upshoot cases. Unlike our study, the observations of Miller, Demer, and Rosenbaum were generated by customized computer software, rather than by a direct visual comparison of the magnetic resonance scans. The results appear comparable for the three different types of Duane's retraction syndrome represented in these investigations in that no large displacement of the lateral rectus muscle was detected. It may be noteworthy that their patient with a bilateral Duane's retraction syndrome had undergone esotropia surgery, of an unspecified nature, on each eye at different times, and a unilateral downshoot did not appear until after the surgical procedure on this affected eye. Miller, Demer, and Rosenbaum suggested that the severing of orbital connective tissues may have permitted the 1- to 2-mm vertical movement of the lateral rectus muscle. In contrast, although neither of our patients had surgery, both demonstrated small displacements of the lateral rectus muscle.

These investigations demonstrate the value of magnetic resonance imaging for the study of motility disorders. Computed tomographic scanning has previously been used to examine patients with strabismus.²⁰ This method requires ionizing radiation, however, which has the potential for damage to the tissues of the eye.²¹ Magnetic resonance imaging uses magnetic field energy and radiofrequency, which produce no known adverse effects. Magnetic resonance imaging is also capable of obtaining

views in any plane of the orbit without the need to reposition the patient. A major limitation of magnetic resonance imaging in the study of ocular movement disorders, however, is its extended data acquisition time, which requires a prolonged period of constant fixation by the subject. Further refinement of magnetic resonance imaging technology may decrease the fixation time needed for these ocular motility studies.

References

1. Huber, A.: Electrophysiology of the retraction syndromes. *Br. J. Ophthalmol.* 58:293, 1974.
2. Kraft, S. P.: A surgical approach for Duane syndrome. *J. Pediatr. Ophthalmol. Strabismus* 25:119, 1988.
3. Parks, M. M., and Eisenbaum, A. M.: Duane's syndrome. What to do and what to expect. *Am. Orthoptic J.* 37:28, 1987.
4. Raab, E. L.: Clinical features of Duane's syndrome. *J. Pediatr. Ophthalmol. Strabismus* 23:64, 1986.
5. Pressman, S. H., and Scott, W. E.: Surgical treatment of Duane's syndrome. *Ophthalmology* 93:29, 1986.
6. Jampolsky, A.: Surgical leashes and reverse leashes in strabismus surgical management. *Transactions of the New Orleans Academy of Ophthalmology. Symposium of Strabismus.* St. Louis, C. V. Mosby, 1978, pp. 252-253.
7. ———: Strategies in strabismus surgery. *Transactions of the New Orleans Academy of Ophthalmology. Pediatric Ophthalmology and Strabismus.* New York, Raven Press, 1986, pp. 381-390.
8. Rogers, G. L., and Bremer, D. L.: Surgical treatment of the upshoot and downshoot in Duane's retraction syndrome. *Ophthalmology* 91:1380, 1984.
9. Miller, J. M., and Robins, D.: Extraocular muscle sideslip and orbital geometry in monkeys. *Vision Res.* 27:381, 1987.
10. Simonsz, H. J., Harting, F., de Waal, B. J., and Verbeeten, B. W. J. M.: Sideways displacement and curved path of recti eye muscles. *Arch. Ophthalmol.* 103:124, 1985.
11. Miller, J. M.: Functional anatomy of normal human rectus muscles. *Vision Res.* 29:223, 1989.
12. Duane, A.: Congenital deficiency of abduction, associated with impairment of adduction, retraction movements, contraction of the palpebral fissure and oblique movements of the eye. *Arch. Ophthalmol.* 34:133, 1905.
13. Scott, A. B., and Wong, G. Y.: Duane's syndrome. An electromyographic study. *Arch. Ophthalmol.* 87:140, 1972.

14. von Noorden, G. K., and Murray, E.: Up- and downshoot in Duane's retraction syndrome. *J. Pediatr. Ophthalmol. Strabismus* 23:212, 1986.
15. Souza-Dias, C.: Additional consequences of muscle co-contraction in Duane's syndrome. *Smith-Kettlewell Symposium on Basic Sciences in Strabismus. V. Congress of CLADE (Conselho Latino-Americano de Estrabismo). São Paulo, Oficinas das Edicoes Loyola, 1978, pp. 93-101.*
16. Scott, A. B.: Upshoots and downshoots. *Smith-Kettlewell Symposium on Basic Sciences in Strabismus. V. Congress of CLADE (Conselho Latino-Americano de Estrabismo). São Paulo, Oficinas das Edicoes Loyola, 1978, pp. 60-65.*
17. Magoon, E., Cruciger, M., Scott, A. B., and Jampolsky, A.: Diagnostic injection of Xylocaine into extraocular muscles. *Ophthalmology* 89:489, 1982.
18. Jampolsky, A.: Muscle slack and EMG misinterpretations in Duane's syndrome and A-V patterns. *ARVO abstracts. Supplement to Invest. Ophthalmol. Vis. Sci. Philadelphia, J. B. Lippincott, 1990, p. 279.*
19. Miller, J. M., Demer, J. L., and Rosenbaum, A. L.: Two mechanisms of up-shoots and downshoots in Duane's syndrome revealed by a new magnetic resonance imaging (MRI) technique. In Campos, E. C. (ed.): *Strabismus and Ocular Motility Disorders. Proceedings of the Sixth Meeting of the International Strabismological Association 1990. New York, Macmillan Publishing, 1991, chap. 34, pp. 229-234.*
20. Saunders, R. A., and Holgate, R. C.: Rectus muscle position in V-pattern strabismus. A study with coronal computed tomography scanning. *Graefes Arch. Clin. Exp. Ophthalmol.* 226:183, 1988.
21. Tomsak, R. L.: Magnetic resonance imaging in neuro-ophthalmology. *Focal Points. Clinical Modules for Ophthalmologists, IV (10). San Francisco, American Academy of Ophthalmology, 1986, p. 7.*

OPHTHALMIC MINIATURE

She was nodding, her rheumy but sharp eyes fixed on his. "Much that comes from Syria is an abomination to me, Empress, as you know, but the poppy is a great blessing. If you were suffering a temporary complaint or were under the power of a curse that I was in the process of lifting I would refuse to let you take any more. . . ." Here he hesitated, but those greying eyes, the whites brown with disease, did not flinch so he continued. ". . . but you are dying, dear Mother. I will order the physician to give you as much poppy as you want."

Pauline Gedge, *Mirage*
New York, Harper Collins, 1990, p. 40

Bilateral Congenital Oculomotor Nerve Palsy in a Child With Brain Anomalies

William V. Good, M.D., A. James Barkovich, M.D., Bonnie L. Nickel, M.D.,
and Creig S. Hoyt, M.D.

We treated a 3-month-old boy with bilateral congenital oculomotor nerve palsy in whom a magnetic resonance imaging scan demonstrated a developmental brain anomaly in the region of the basal ganglia. The pupil was normal on one side, and there was no aberrant regeneration of the oculomotor nerve. We could find no evidence for a peripheral oculomotor nerve lesion. This demonstrates that congenital oculomotor nerve palsy can be caused by brainstem disease. Embryologically, basal ganglia and oculomotor nuclei develop at the same time, and the Edinger-Westphal nucleus develops later. Thus, pupil sparing does not exclude a central origin for congenital oculomotor nerve palsy.

ISOLATED OCULOMOTOR NERVE PALSY in children is uncommon compared to adults^{1,2} and often congenital in nature. The location of the lesion causing the congenital oculomotor palsy has been presumed to be in the peripheral nerve on the basis of two clinical observations: aberrant regeneration of the oculomotor nerve occurs commonly in congenital and traumatic cases³; and associated neurologic problems in children with oculomotor nerve palsy are uncommon,⁴ although this observation has been challenged.⁵

We treated a child with congenital, bilateral oculomotor palsy in whom a magnetic resonance imaging scan showed aplasia of basal ganglia structures on one side. The small size of extraocular muscles innervated by this nerve also suggests that oculomotor nerve nucleus

hypoplasia or aplasia was the cause of this child's oculomotor palsy.

Case Report

A 3-month-old boy was examined in consultation at the University of California, San Francisco, for exotropia and bilateral blepharoptosis. There was no history of birth trauma. The patient was a full-term infant, and his developmental milestones were normal for his age.

Examination showed an alert and smiling infant. The right eye had blepharoptosis, but the pupil was not covered. He was unable to adduct, elevate, or depress the eye. The pupil was 2 mm and reactive. The left eye showed mild blepharoptosis, and again, the pupil was not occluded. Adduction of the left eye was 50% of normal, and he was unable to elevate or depress the left eye. The pupil was 5 mm dilated and weakly reactive to light. Neither eye showed signs of aberrant regeneration of the oculomotor nerve. Other cranial nerves were intact.

A magnetic resonance imaging scan demonstrated an absent caudate and lentiform nucleus on the right (Fig. 1). The absence of cysts or high signal intensity in the region of the basal ganglia on the T₂-weighted image indicated early damage to or aplasia or hypoplasia of the structures, as opposed to secondary destruction during late gestation or at birth. The right frontal horn was dilated secondary to caudate nucleus aplasia (Fig. 2). The internal capsule appeared normal bilaterally.

Coronal views of the orbits showed hypoplasia of extraocular muscles innervated by the oculomotor nerve (Fig. 3). The right muscles appeared to be more affected than the left, consistent with the physical examination, in which the right blepharoptosis and ocular

Accepted for publication Jan. 2, 1991.

From the Departments of Ophthalmology (Drs. Good and Hoyt) and Radiology (Dr. Barkovich), University of California, San Francisco, California. Dr. Nickel is in private practice in San Rafael, California.

Reprint requests to William V. Good, M.D., 400 Parassus Ave., A 704, San Francisco, CA 94143.

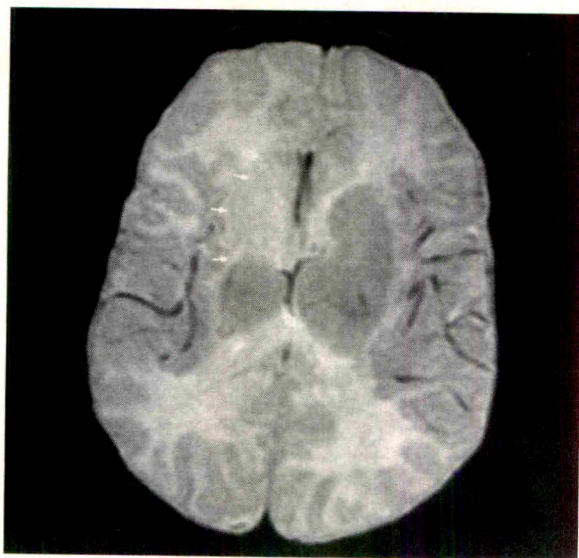


Fig. 1 (Good and associates). T₂-weighted image shows normal caudate, lentiform, and thalamus structures on the left. On the right, the caudate and lentiform nuclei are gone (arrows). The absence of bright signal in the region of the basal ganglia indicates that this is not a destructive process.

movements were worse than the left. The lateral recti and superior oblique muscles appeared normal.

Discussion

An intra-axial (brainstem) anomaly was the most likely cause of this child's bilateral oculomotor nerve palsy. The perinatal history was unremarkable, which suggested that trauma probably was not a factor in the oculomotor nerve palsy. There was no aberrant regeneration of the oculomotor nerve (synkinesis), a finding that usually occurs with peripheral oculomotor nerve lesions.³ The magnetic resonance imaging scan showed an absence of basal ganglia structures on the side with the most severe involvement. The T₂-weighted image showed no bright signal in this region, which excluded an injury after the 20th gestational week.

Demonstration of a central cause for oculomotor nerve palsy in congenital cases is difficult. Most children with congenital oculomotor nerve palsy survive into adulthood, which has resulted in a scarcity of pathologic material. Nevertheless, Wibrand and Saenger⁶ reported one case of hypoplasia of a portion of the oculomotor nucleus. Other cranial nerves were



Fig. 2 (Good and associates). T₁-weighted image shows a dilated right frontal horn caused by absence of the caudate nucleus (small arrow). The high signal intensity (large arrows) of the posterior limb of the internal capsule is normal bilaterally.

also affected. Norman⁷ described an infant with a unilateral oculomotor nerve palsy caused by a nonocclusive thrombus of the basilar artery. A patient described by Papst and Esslen⁸ had hypoplasia of oculomotor nerve nuclei and bilateral facial nerve palsy. Miller⁹ described a patient in whom hypoplasia of oculomotor nerve nuclei was accompanied by digital anomalies and mental retardation.

Most cases of congenital oculomotor palsy are unilateral. Two cases reported by Reinecke¹⁰ and one by Balkan and Hoyt⁵ were bilateral. The patient of Balkan and Hoyt had a Marcus Gunn jaw wink phenomenon, developmental delays, and a normal labor and delivery. The jaw winking implied a condition that was central rather than peripheral. We agree that congenital oculomotor nerve palsy can be caused by peripheral lesions during parturition; however, the likelihood of isolated bilateral involvement without other obvious neurologic damage caused by birth trauma seems remote and should suggest a central mechanism.

In our patient, the right pupil was not involved and the left was partially affected. In the studies by Victor³ and Miller,⁴ all patients had pupillary involvement, but sometimes the pupil was miotic because of aberrant regeneration. Four of the patients of Balkan and

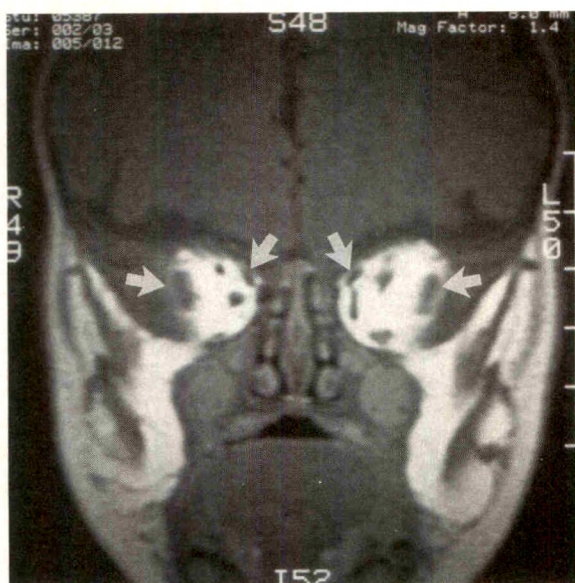


Fig. 3 (Good and associates). Coronal view of the globes and extraocular muscles. Note that muscles innervated by the oculomotor nerve are small compared to the lateral rectus and superior oblique muscles (arrows). On the right, the medial rectus muscle cannot be identified.

Hoyt⁵ showed no pupillary abnormality. In adults, pupil sparing oculomotor nerve palsy is usually caused by sparing of the pupillomotor fibers in microvascular infarcts of the extra-axial nerve.^{11,12} Nadeau and Trobe,¹³ however, described pupil sparing oculomotor nerve palsy caused by midbrain infarction and brainstem glioma. Other reports described pupillary sparing with infarction of the brainstem¹⁴ and infiltration of the brainstem by tumor.^{15,16} It seems that pupillary sparing in congenital oculomotor nerve palsy, therefore, is the exception but does not preclude a central origin.

The embryologic characteristics of the oculomotor nucleus support the possibility of a pupil sparing, central oculomotor nerve palsy. Oculomotor nerve nuclei form during the fifth gestational week. The globus pallidus and striatum form at the same time.¹⁷ A fifth-gestational week event could damage oculomotor nerve nuclei and basal ganglia structures. The Edinger-Westphal nucleus does not become distinguishable until the tenth or 11th gestational week. It could be spared or partially spared in the event of earlier damage.

The extraocular muscles innervated by the oculomotor nerve were small in both eyes of our patient (Fig. 3). The muscles of the right eye were smaller than those of the left eye, with the

right medial rectus muscle virtually absent. Standards for normal-size muscles do not exist, but the superior oblique and lateral recti muscles, innervated by the trochlear and abducens cranial nerves, respectively, were much larger. Embryologically, the extraocular muscles form at five weeks. Nuclei of the oculomotor nerve can be identified in the mesencephalic tegmentum by the fifth week.¹⁷ Oculomotor nerve fibers emerge from the brainstem at six weeks and reach appropriate extraocular muscles thereafter. The extremely small size of extraocular muscles in this scan (Fig. 3), which was taken at an early age, implies a prenatal disease process and the possibility that some of these muscles, particularly on the right, never received any innervation. Horton and associates¹⁸ documented a decrease in the size of extraocular muscles in acquired cranial nerve palsy. In our patient, however, the muscles innervated by the oculomotor nerves were extremely small, and the right medial rectus muscle was virtually absent.

This case demonstrates that congenital oculomotor nerve palsy can be caused by developmental anomalies of the brain. We agree with Balkan and Hoyt⁵ that other neurologic abnormalities can accompany congenital oculomotor nerve palsy. Magnetic resonance imaging scanning in patients with congenital oculomotor nerve palsy may identify children at risk for neurologic problems. Since extraocular muscles can be hypoplastic, scanning may also allow the strabismus surgeon to formulate a realistic treatment plan.

References

1. Rucker, C. W.: Paralysis of the third, fourth, and sixth cranial nerves. *Am. J. Ophthalmol.* 46:787, 1958.
2. ———: The causes of paralysis of third, fourth, and sixth cranial nerves. *Am. J. Ophthalmol.* 61:1293, 1966.
3. Victor, D. I.: The diagnosis of congenital unilateral third nerve palsy. *Brain* 99:7111, 1976.
4. Miller, N. R.: Solitary oculomotor nerve palsy in childhood. *Am. J. Ophthalmol.* 83:106, 1977.
5. Balkan, R., and Hoyt, C. S.: Associated neurologic abnormalities in congenital third nerve palsies. *Am. J. Ophthalmol.* 97:315, 1984.
6. Wilbrand, H. O., and Saenger, A.: Die kongenitalen augenmuskellähmungen (kernaplasie) in der. *Neurol. Auges* 8:179, 1924.
7. Norman, M. G.: Unilateral encephalomalacia in

cranial nerve nuclei in neonates. Report of two cases. *Neurology* 24:424, 1974.

8. Papst, W., and Esslen, E.: Elektromyographischer beitrage zum Möbius syndrom. *Klin. Monatsbl. Augenheilkd.* 137:401, 1960.

9. Miller, N. R.: Walsh and Hoyt's *Clinical Neuro-ophthalmology*, ed. 4, vol. 2. Baltimore, Williams and Wilkins, 1985, p. 653.

10. Reinecke, R. D.: Surgical results of third cranial nerve palsies. *N.Y. State J. Med.* 72:1255, 1972.

11. Dreyfus, P. M., Hakim, S., and Adams, R. D.: Diabetic ophthalmoplegia. *Arch. Neurol. Psychiatry* 77:337, 1957.

12. Asbury, A. K., Audredge, H., and Hershberg, R.: Oculomotor palsy in diabetics. A clinicopathological study. *Brain* 93:555, 1970.

13. Nadeau, S. E., and Trobe, J. D.: Pupil-sparing in oculomotor palsy. A brief review. *Ann. Neurol.* 13:143, 1983.

14. Starr, N. A.: Ophthalmoplegia externa partialis. *J. Nerv. Ment. Dis.* 13:300, 1888.

15. Gonyea, E. F., and Collins, J. H.: Neuro-ophthalmic pathological correlates in primary reticulum cell sarcoma of the nervous system. *J. Neurol. Neurosurg. Psychiatry* 37:1005, 1974.

16. Wilkins, D. E., and Samhour, A. M.: Isolated bilateral oculomotor paresis due to lymphoma. *Neurology* 28:1425, 1979.

17. Sidman, R. L., and Rokic, P.: Development of the human central nervous system. In Haymaker, W., and Adams, R. D. (eds.): *Histology and Histopathology of the Nervous System*. Springfield, Charles C Thomas, 1982, pp. 3-145.

18. Horton, J. C., Tsai, R.-K., Truwit, C. L., and Hoyt, W. F.: Magnetic resonance imaging of superior oblique muscle atrophy in acquired trochlear nerve palsy. *Am. J. Ophthalmol.* 110:315, 1990.

OPHTHALMIC MINIATURE

Mostly these days when I go to the beach I just stay out of the water altogether. I sit on the shore and play cretin, sand-digging games with my three-year-old son, and I watch the lifeguards, who sit way up on the beach with their 20-20 vision and blow their whistles at swimmers I couldn't see even with the aid of a radio telescope, off the coast of France somewhere.

Dave Barry, *Dave Barry's Greatest Hits*
New York, Fawcett Columbine, 1988, p. 25

Correlation of the Blind Spot Size to the Area of the Optic Disk and Parapapillary Atrophy

Jost B. Jonas, M.D., Gabriele C. Gusek, M.D., and Martin C. Fernández, M.D.

We evaluated the relationship between the optic disk and the blind spot area. Using kinetic Goldmann perimetry in 23 patients with open-angle glaucoma and 19 normal subjects, the blind spot size was correlated significantly with the total area of the optic disk, peripapillary scleral ring, and parapapillary chorioretinal atrophy. Zone Beta of the parapapillary atrophy with a visible sclera was attributed to an absolute scotoma, and zone Alpha with irregular pigmentation was attributed to a relative scotoma. The blind spot was significantly larger in the glaucomatous eyes than in the normal eyes, which corresponded with a larger zone Beta in the glaucomatous eyes. The intrapapillary and parapapillary region of the optic nerve head correlated to the size of the blind spot, which included the parapapillary chorioretinal atrophy and a significant size difference between normal and glaucomatous eyes.

THE OPTIC NERVE HEAD represents the morphologic correlate of the blind spot in the visual field. The interindividual variability of its area was previously measured to range between 0.8 and 5.5 mm² in normal eyes.¹ The chorioretinal atrophy bordering the optic disk (Figs. 1 and 2) also differs considerably in size, frequency, and shape.²⁻¹¹ Parapapillary chorioretinal atrophy has been reported to be more common and larger in glaucomatous eyes than in normal eyes or eyes with ocular hypertension.^{2-4,7-11} The

association between the parapapillary alterations and the glaucomatous damage does not indicate that these changes are necessarily either causes or effects in the pathogenesis of glaucoma.^{7,8} The parapapillary chorioretinal changes are associated with a decreased count of retinal photoreceptors.¹¹ The interindividual variability in the size of the optic disk and parapapillary chorioretinal atrophy could lead one to the assumption that the blind spot, too, is subject to interindividual variation, which may render the detection of a glaucomatous enlargement difficult.

Traquair¹²⁻¹⁴ introduced a depression of the central isopter known as "baring of the blind spot" as an early change of chronic simple glaucoma. Drance,¹⁵ however, pointed out that most of Traquair's patients had angle-closure glaucoma, and he assumed that many of them probably already had prodromal symptoms of angle-closure glaucoma before the commencement of the study. Reporting his own findings that barring of the blind spot could be produced

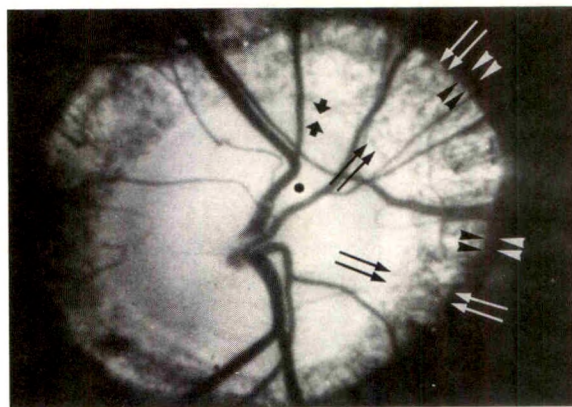


Fig. 1 (Jonas, Gusek, and Fernández). Glaucomatous optic nerve head. Disk area, 6.40 mm²; zone Beta (between long double arrows), 8.03 mm²; zone Alpha (between double arrowheads) of the parapapillary chorioretinal atrophy, 2.50 mm²; peripapillary scleral ring (black short arrows), 0.50 mm². Black point, photographic artifact.

Accepted for publication Jan. 18, 1991.

From the Department of Ophthalmology, University Eye Hospital, University Erlangen-Nürnberg, Germany. This study was supported by funds from Dr. Helmut und Margarete Meyer-Schwartz Stiftung, Deutsche Forschungsgemeinschaft DFG (grant Na 55/6-1/Jo), and H. Förderverein Ophthalmologie, Erlangen-Nürnberg.

Reprint requests to Jost B. Jonas, M.D., University Eye Hospital, Schwabachanlage 6, D-8520 Erlangen, Germany.

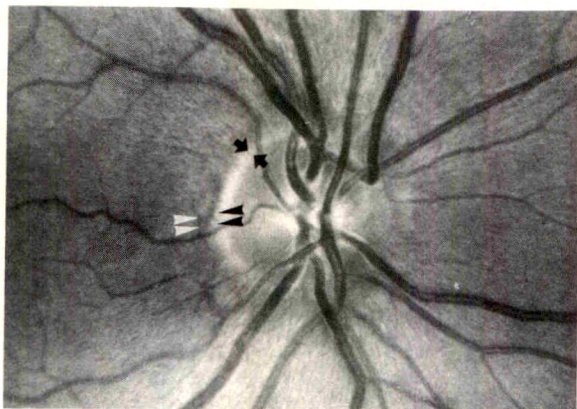


Fig. 2 (Jonas, Gusek, and Fernández). Normal optic nerve head. Disk area, 1.83 mm²; no zone Beta; zone Alpha (between double arrowheads), 0.15 mm²; peripapillary scleral ring (black short arrows), 0.20 mm². Note marked difference in the visibility of the retinal nerve fiber bundles in Figures 1 and 2.

also in normal subjects, Drance did not consider this sign to be pathognomonic for glaucoma.

Aulhorn and Harms,¹⁶ Drance,¹⁷ and Drance, Wheeler, and Pattulo¹⁸ showed that the area around the blind spot had the flattest slope so that threshold targets could be made to bare the blind spot in a nonspecific way. Armaly¹⁹ pointed out that the parapapillary region, especially at the superior and inferior disk poles, was less sensitive than the surrounding retina. He did not exclude the possibility that such defects also might be caused by a glaucomatous process. The perimetric changes close to the blind spot, however, were common also in normal subjects after the age of 40 years and were markedly influenced by slight changes in refraction and in lens opacities. Because of this, Armaly¹⁹ precluded the use of pericentral scotomata as perimetric criteria of glaucoma.

Hart and Becker²⁰ described that in 29 of 98 eyes (30%) with initial glaucomatous defects the blind spot showed an arcuate enlargement and that the most common area for paracentral disturbances was adjacent to the superonasal pole of the blind spot. Using computerized perimetry, Gramer and associates²¹ described an enlargement of the blind spot as an early perimetric sign of glaucoma. However, they did not use a special program for measuring the blind spot. Many other investigators have not considered an increase in the blind spot size as characteristic for glaucoma.²²⁻²⁴

Considering this diversity of opinions, the aims of our study were the following: determi-

nation of correlations between the blind spot size and the areas of the optic disk, peripapillary scleral ring, and parapapillary chorioretinal atrophy (Figs. 1 and 2), if any; detection of possible association of the parapapillary chorioretinal atrophy with a relative or absolute scotoma; and testing of the hypothesis that normal and glaucomatous eyes differ in the blind spot size, taking into account the area of the optic disk and parapapillary chorioretinal atrophy.

Patients and Methods

We studied 579 eyes of 323 patients with open-angle glaucoma and 24 normal eyes of 19 subjects. Selection criteria for the diagnosis of glaucoma were an open anterior chamber angle, intraocular pressure readings exceeding 21 mm Hg, glaucomatous changes of the optic disk, and visual field defects. Visual field defects included isolated or confluent paracentral scotomata, a nasal step of at least ten degrees, and abnormally high visual field indices on automated perimetry. The subjects of the control group came to our institution for a regular ocular examination, prescription of spectacles, or diseases of the fellow eye, which was not included in the study. These diseases, such as perforating corneal injuries, did not primarily affect the optic nerve.

For all eyes, 15-degree color stereoscopic optic disk diapositives were taken with an Allen stereoscopic separator and a telecentric fundus camera. The diapositives were projected in a magnification scale of 1 to 15. The outlines of the optic disk, peripapillary scleral ring, and parapapillary chorioretinal atrophy were plotted on paper and analyzed morphometrically. The outer border of the optic disk was identical with the inner border of the peripapillary scleral ring. The parapapillary chorioretinal atrophy⁹⁻¹¹ was divided into a peripheral zone (zone Alpha), characterized by irregular hypopigmentation and hyperpigmentation, and a second zone (zone Beta), located close to the peripapillary scleral ring and with a sclera and large choroidal vessels visible upon ophthalmoscopy (Figs. 1 and 2). To obtain measurements in absolute size units (millimeters and square millimeters), the photographic magnification was corrected according to Littmann's method,²⁵ which took into account the anterior corneal curvature and refractive error.

Using the III_{4e} , I_{4e} , I_{3e} , and I_{2e} isopters and Goldmann's kinetic perimetry, we evaluated the size of the blind spot in 44 eyes of 23 patients (14 women, nine men; age, 55.0 ± 12.5 years, range, 28 to 74 years; refractive error, -1.51 ± 3.2 diopters, range, -13.0 to $+1.6$ diopters) and in 24 normal eyes of 19 subjects (eight women, 11 men; age, 50.1 ± 12.4 years, range, 17 to 67 years; refractive error, -0.66 ± 2.53 diopters, range, -8.1 to $+2.1$ diopters). The area covered by each isopter on the visual field chart was measured with a planimeter in square millimeters. The differential areas between the isopters were calculated by subtraction. In a second step, the values were corrected for the ocular magnification taking into account the same Littmann factor that was used for determination of the papillomorphometric data. This correction resulted in a mathematic enlargement of the blind spot in myopic eyes and a mathematic decrease of blind spot area in hyperopic eyes.

With the Octopus program G1, the blind spot was determined in 535 eyes of 301 patients with glaucoma (159 women, 142 men; age, 63.0 ± 12.8 years, range, 15 to 91 years; refractive error, -1.0 ± 1.90 diopters, range, -14.75 to $+6.4$ diopters). The blind spot was considered to be generally enlarged if at least three of ten points surrounding the blind spot showed a relative or absolute scotoma. The blind spot was thought to be enlarged in its superior, inferior, temporal, or nasal half if at least 50% of the points located in that region had a decreased light differential threshold.

The evaluation of the blind spot was performed without previous knowledge of the optic disk morphologic characteristics. For inter-individual comparison, only one randomly selected eye per subject and patient was taken for statistical analysis. For determination of differences between the right and left sides, both eyes of the same individual were included in the statistical process.

Results

In the normal group, the total areas of the optic disk, peripapillary scleral ring, and zones Alpha and Beta of the parapapillary chorioretinal atrophy were correlated significantly with the areas of all isopters tested (correlation coefficients ranging between .63 and .93; $P < .0001$). The coefficients were highest for the

correlation with isopters III_{4e} and I_{4e} and lowest for isopter I_{2e} . The same was true if the area of zone Alpha was kept out of the total. The correlation coefficients and the P values did not vary significantly as compared to the total area including zone Alpha. The combined area of the optic disk and peripapillary scleral ring was not correlated significantly with the other isopters and only marginally correlated ($P = .08$) with isopter III_{4e} . The optic disk and the peripapillary scleral ring taken separately were not correlated with any perimetric factor.

If the areas between the isopters were considered, the size of zones Alpha and Beta was not significantly correlated with any differential area with the exception of a marginally significant correlation to the differential area between the isopters III_{4e} and I_{4e} (correlation coefficient, $r = .41$; $P = .08$). The areas of the optic disk and peripapillary scleral ring were not correlated with any differential area between the isopters.

In the glaucomatous eyes also, the combined areas of the papillomorphometric variables, whether zone Alpha was included or not, were significantly correlated with the areas of all isopters (correlation coefficients ranging between .36 and .59; $P < .05$). Again, the coefficients and the P values ($P < .001$) were highest for the correlation with isopters III_{4e} and I_{4e} . The areas of the papillomorphometric factors by themselves were not correlated significantly with any differential area between the isopters. There was a tendency, however, that the areas of zones Alpha and Beta were correlated with the differential area between the isopters III_{4e} and I_{4e} .

With all patients and subjects taken into account, the total area of the optic disk, peripapillary scleral ring, and parapapillary chorioretinal atrophy, including and excluding zone Alpha, was best correlated with the size of isopters I_{4e} (Fig. 3) and III_{4e} (Fig. 4) (Table 1). Additionally, if zone Beta was excluded, the combined area of the optic disk and peripapillary scleral ring as well as the optic disk area taken separately were also best correlated to isopter III_{4e} (Fig. 5). The coefficients and significance, however, were lower in this case as compared to the correlation between isopter III_{4e} and the total area including zone Beta (Table 1). Concerning the differential areas between the isopters, both zones Alpha and Beta were correlated with the differential area between isopters III_{4e} and I_{4e} (Figs. 6 and 7). The peripapillary scleral ring, the optic disk, and the sum of these two variables did not show any

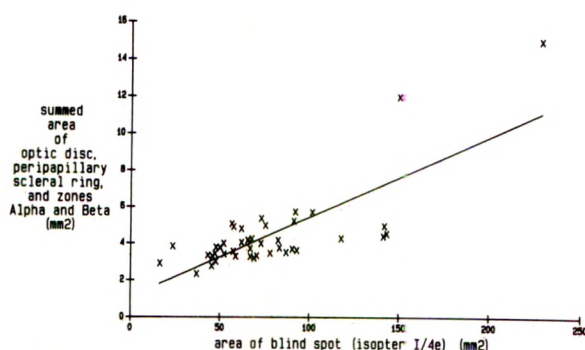


Fig. 3 (Jonas, Gusek, and Fernández). Scattergram showing the correlation between the combined areas of the optic disk, peripapillary scleral ring, and zones Alpha and Beta of the parapapillary chorioretinal atrophy and the size of isopter I_{4e} taken for determination of the blind spot. Correlation coefficient, $r = .77$; $P < .001$.

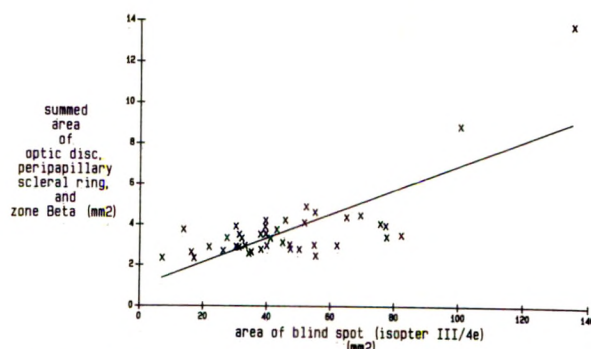


Fig. 4 (Jonas, Gusek, and Fernández). Scattergram showing the correlation between the combined areas of the optic disk, peripapillary scleral ring, and zone Beta of the parapapillary chorioretinal atrophy and the size of isopter III_{4e} taken for determination of the blind spot. Correlation coefficient, $r = .76$; $P < .001$.

significant relationships to any differential area between the isopters (Table 1).

In intraindividual bilateral comparison, the difference between both sides (right eye minus left eye) in the papillomorphometric data were significantly correlated with the difference be-

tween both sides in the area of the isopters III_{4e} to I_{2e} .

Upon comparison of the glaucoma and normal groups for age ($P = .09$), refractive error ($P = .12$), sex, and the areas of the optic disk, peripapillary scleral ring, and zone Alpha, the

TABLE 1
COEFFICIENTS AND SIGNIFICANCE OF CORRELATIONS BETWEEN MORPHOMETRIC DATA OF THE OPTIC DISK AND PERIMETRIC DATA OF THE BLIND SPOT*

ISOPTER	OPTIC DISK, PERIPAPILLARY SCLERAL RING, ZONE BETA, ZONE ALPHA		OPTIC DISK, PERIPAPILLARY SCLERAL RING, ZONE BETA		OPTIC DISK, PERIPAPILLARY SCLERAL RING		OPTIC DISK		PERIPAPILLARY SCLERAL RING		ZONE BETA		ZONE ALPHA	
	r	P VALUE	r	P VALUE	r	P VALUE	r	P VALUE	r	P VALUE	r	P VALUE	r	P VALUE
III_{4e}	.77	<.001	.76	<.001	.48	<.01	.46	<.01	NS	NS	.68	<.001	.52	<.001
I_{4e}	.77	<.001	.76	<.001	.40	<.01	.38	<.05	NS	NS	.72	<.001	.48	<.01
I_{3e}	.54	<.001	.51	<.001	.35	<.05	.35	<.05	NS	NS	.45	<.01	.42	<.01
I_{2e}	.54	<.001	.50	<.001	.41	<.01	.39	<.05	NS	NS	.42	<.01	.46	<.01
$III_{4e} - I_{4e}$.59	<.001	.59	<.001	NS	NS	NS	NS	NS	NS	.60	<.001	.34	<.05
$III_{4e} - I_{3e}$	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	.18	.27	.09
$III_{4e} - I_{2e}$	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	.40	.30	.05
$I_{4e} - I_{3e}$	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
$I_{4e} - I_{2e}$	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
$I_{3e} - I_{2e}$	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS

*NS indicates not significant.

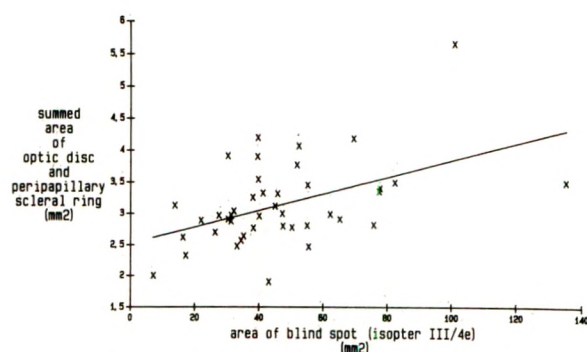


Fig. 5 (Jonas, Gusek, and Fernández). Scattergram showing the correlation between the combined area of the optic disk and the peripapillary scleral ring and the size of the blind spot measured by Goldmann's kinetic perimetry using the isopter III_{4e}. Correlation coefficient, $r = .48$; $P = .001$.

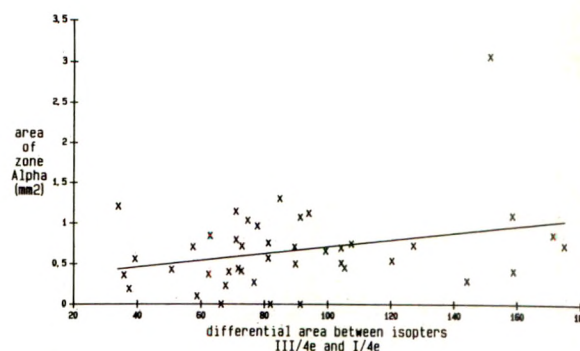


Fig. 6 (Jonas, Gusek, and Fernández). Scattergram showing the correlation between the area of zone Alpha of the parapapillary chorioretinal atrophy and the differential area between the isopters III_{4e} and I_{4e} taken for determination of the blind spot. Correlation coefficient, $r = .34$; $P < .05$.

differences were not significant (Table 2). For this purpose, severely myopic eyes with a myopic refractive error of more than -8 diopters were excluded. The glaucoma group consisted then of 22 patients and the control group of 18 subjects. Zone Beta, the size of the isopters I_{4e}, I_{3e}, and I_{2e}, and the differential areas between the isopters were significantly larger in the glaucomatous eyes. Isopter III_{4e} was larger but not significantly larger in the glaucomatous eyes (Table 2).

If the blind spot values were corrected for the ocular magnification, the correlation coefficients and the significances were higher and the differences in the perimetric variables between the glaucoma and normal group reached a greater level of significance than for uncorrected data.

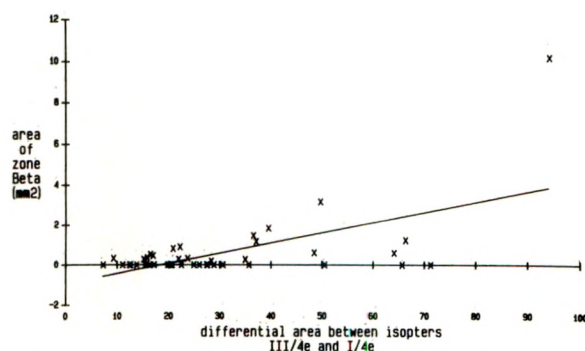


Fig. 7 (Jonas, Gusek, and Fernández). Scattergram showing the correlation between the area of zone Beta of the parapapillary chorioretinal atrophy and the differential area between the isopters III_{4e} and I_{4e} taken for determination of the blind spot. Correlation coefficient, $r = .60$; $P < .001$.

TABLE 2
MORPHOMETRIC DATA OF THE OPTIC NERVE HEAD
AND PERIMETRIC DATA OF THE BLIND SPOT

AREA (MM ²)	NORMAL EYES (N = 18)	GLAUCOMA EYES (N = 22)	P VALUE
Optic disk	2.70 ± 0.49	2.61 ± 0.51	.91
Peripapillary scleral ring	0.36 ± 0.11	0.47 ± 0.26	.15
Zone Alpha	0.59 ± 0.29	0.60 ± 0.38	.77
Zone Beta	0.08 ± 0.15	0.48 ± 0.56	<.01
Optic disk and peripapillary ring	3.06 ± 0.55	3.08 ± 0.55	.41
Optic disk, peripapillary ring, and zone Beta	3.13 ± 0.60	3.55 ± 0.69	<.05
Optic disk, peripapillary ring, zone Beta, and zone Alpha	3.72 ± 0.68	4.16 ± 0.87	<.05
Isopter III _{4e}	39.2 ± 11.9	46.1 ± 21.8	.29
Isopter I _{4e}	59.9 ± 17.0	79.8 ± 33.9	<.05
Isopter I _{3e}	83.9 ± 27.6	123.0 ± 61.5	<.05
Isopter I _{2e}	111.8 ± 36.0	145.6 ± 48.5	<.01
Differential area between isopters			
III _{4e} -I _{4e}	20.7 ± 10.0	33.7 ± 18.5	<.05
III _{4e} -I _{3e}	44.7 ± 23.7	76.9 ± 48.2	<.01
III _{4e} -I _{2e}	72.6 ± 32.4	99.4 ± 34.4	<.01
I _{4e} -I _{3e}	24.0 ± 15.3	43.2 ± 36.1	<.01
I _{4e} -I _{2e}	51.8 ± 23.1	65.7 ± 22.0	<.05
I _{3e} -I _{2e}	27.8 ± 19.4	22.5 ± 36.8	.14

were not correlated significantly with the areas of the optic disk, peripapillary scleral ring, and parapapillary chorioretinal atrophy, either totally or separately.

Discussion

Defining the blind spot as absolute and relative scotoma as determined by the isopters III_{4e} and I_{4e} to I_{2e}, respectively, its size was correlated positively with the area of the optic disk and parapapillary chorioretinal atrophy (Table 1, Figs. 3 through 7). The blind spot was large in eyes with a large optic disk and a marked parapapillary chorioretinal atrophy. Conversely, eyes with small optic nerve heads with an unremarkable surrounding region had small blind spots. The interindividual variability in the size of the blind spot, already reported by Wentworth²⁶ in 1931, was in direct proportion to the variation in the combined areas of the optic disk, peripapillary scleral ring, and parapapillary chorioretinal atrophy.

This relationship between the size of the blind spot and the papillomorphometric variables prompts one to question which regions of the optic nerve head could possibly correspond to a particular isopter. The isopters III_{4e} and I_{4e} had the highest correlation coefficients and the lowest P values. The correlations were least significant for isopters I_{3e} and I_{2e}. Concerning the differential areas, the region between isopters III_{4e} and I_{4e} showed the most significant relationships. It was best correlated with zone Beta followed by zone Alpha of the parapapillary chorioretinal atrophy. The differential areas between isopters III_{4e} and I_{3e} and between isopters III_{4e} and I_{2e} were correlated marginally with zone Alpha but not with zone Beta (Table 1). All other differential areas between other isopters were not correlated with any papillomorphometric variable (Table 1).

These factors could lead to the hypothesis that zone Beta, characterized by visible sclera, is associated with an absolute scotoma and that zone Alpha could correspond to a relative scotoma with retinal differential light thresholds ranging between isopters III_{4e} and I_{2e}. The correlation of zone Beta with the differential area between the isopters III_{4e} and I_{4e} leaves it unclear whether the peripheral part of zone Beta is associated additionally with a relative scotoma. The hypothesis is in agreement with morpho-

logic studies, which suggest that zone Beta perhaps correlates histologically with a region that is characterized by the absence of retinal pigment epithelium cells and by retinal photoreceptors being absent close to the optic disk and markedly reduced in number peripherally. Zone Alpha could histologically represent irregularities of the retinal pigment epithelium and a thinning, but not a complete loss, of the outer retinal layer.¹¹ This is in agreement with the study of Stürmer, Schroedel, and Rappl,²⁷ which reported that, in direct laser scanning perimetry of the fundus, zone Beta represented an absolute scotoma and zone Alpha represented a relative scotoma.

The blind spot was significantly larger in the glaucomatous eyes than in the control group (Table 2). For this comparison, severely myopic eyes with a myopic refractive error of more than -8 diopters were excluded, and both groups were matched for refractive error. Correspondingly, the glaucoma and normal groups varied significantly in the area of zone Beta and in the summed area of the optic disk, peripapillary scleral ring, and total parapapillary chorioretinal atrophy (Table 2).

The perimetric data were generally better correlated when they had been corrected for the ocular magnification using Littmann's method.²⁵ For interindividual comparison of the area of visual field defects, the refractive error may therefore be an important factor to be considered.

The data of the blind spot obtained with the Octopus program G1 were not correlated statistically with the papillomorphometric variables, which show that program G1 is not suitable for detection of a glaucomatous enlargement of the blind spot. This is in agreement with the design of the program.

References

1. Jonas, J. B., Gusek, G. C., and Naumann, G. O. H.: Optic disk, cup, and neuroretinal rim size, configuration, and correlations in normal eyes. *Invest. Ophthalmol. Vis. Sci.* 29:1151, 1988.
2. Primrose, J.: Early signs of the glaucomatous disc. *Br. J. Ophthalmol.* 55:820, 1971.
3. Wilensky, J. T., and Kolker, A. E.: Peripapillary changes in glaucoma. *Am. J. Ophthalmol.* 81:341, 1976.
4. Airaksinen, P. J., Juvala, P. A., Tuulonen, A., Alanko, A. I., Valkonen, R., and Tuohino, A.: Change

of peripapillary atrophy in glaucoma. In Krieglstein, G. K. (ed.): *Glaucoma Update III*. Berlin, Springer-Verlag, 1987, pp. 97-102.

5. Fantes, F. E., and Anderson, D. R.: Clinical histologic correlation of human peripapillary anatomy. *Ophthalmology* 96:20, 1989.

6. Nevarez, J., Rockwood, E. J., and Anderson, D. R.: The configuration of peripapillary tissue in unilateral glaucoma. *Arch. Ophthalmol.* 106:901, 1988.

7. Rockwood, E. J., and Anderson, D. R.: Acquired peripapillary changes and progression in glaucoma. *Graefes Arch. Clin. Exp. Ophthalmol.* 226:510, 1988.

8. Buus, D. R., and Anderson, D. R.: Peripapillary crescents and halos in normal-tension glaucoma and ocular hypertension. *Ophthalmology* 96:16, 1989.

9. Jonas, J. B., Nguyen, N. X., Gusek, G. C., and Naumann, G. O. H.: Parapapillary chorioretinal atrophy in normal and glaucoma eyes. I. Morphometric data. *Invest. Ophthalmol. Vis. Sci.* 30:908, 1989.

10. Jonas, J. B., and Naumann, G. O. H.: Parapapillary chorioretinal atrophy in normal and glaucoma eyes. II. Correlations. *Invest. Ophthalmol. Vis. Sci.* 30:919, 1989.

11. Jonas, J. B., Königsreuther, K. A., and Naumann, G. O. H.: Histomorphometry of the parapapillary region in glaucomatous and normal human eyes. *ARVO abstracts. Supplement to Invest. Ophthalmol. Vis. Sci. Philadelphia, J. B. Lippincott*, 1990, p. 456.

12. Traquair, H. M.: Glaucoma with special reference to medical aspects and early diagnosis. *Br. Med. J.* 3906:922, 1935.

13. ———: Clinical detection of early changes in the visual field. *Am. Arch. Ophthalmol.* 22:947, 1939.

14. ———: Perimetry in the study of glaucoma. *Trans. Ophthalmol. Soc. U.K.* 51:585, 1948.

15. Drance, S. M.: The early field defects in glaucoma. *Invest. Ophthalmol.* 8:84, 1969.

16. Aulhorn, E., and Harms, H.: Early visual field defects in glaucoma. In Leydhecker, W. (ed.): *Glaucoma. Tützing Symposium 1966*. Basel, Karger, 1967 pp. 151-186.

17. Drance, S. M.: The glaucomatous visual field. *Br. J. Ophthalmol.* 56:186, 1972.

18. Drance, S. M., Wheeler, C., and Pattulo, M.: The use of static perimetry in the early detection of glaucoma. *Can. J. Ophthalmol.* 2:249, 1967.

19. Armaly, M. F.: The size and location of the normal blind spot. *Arch. Ophthalmol.* 81:192, 1969.

20. Hart, W. M., and Becker, B.: The onset and evolution of glaucomatous visual field defects. *Ophthalmology* 89:268, 1982.

21. Gramer, E., Gerlach, R., Krieglstein, G. K., and Leydhecker, W.: Zur Topographie früher glaukomatöser Gesichtsausfälle bei der Computerperimetrie. *Klin. Monatsbl. Augenheilkd.* 180:515, 1982.

22. Shields, M. B.: *Textbook of Glaucoma*. Baltimore, Williams and Wilkins, 1987, p. 107.

23. Heijl, A.: Strategies for detection of glaucoma defects. In Drance, S. M., and Anderson, D. R.: *Automatic Perimetry in Glaucoma. A Practical Guide*. Orlando, Grune and Stratton, 1985, p. 44.

24. Greve, E. L., Langerhorst, C. T., and van den Berg, T. T. J. P.: Perimetry and other visual function tests in glaucoma. In Cairns, J. E. (ed.): *Glaucoma*. London, Grune and Stratton, 1986, p. 56.

25. Littmann, H.: Zur Bestimmung der wahren Größe eines Objektes auf dem Hintergrund des lebenden Auges. *Klin. Monatsbl. Augenheilkd.* 180:286, 1982.

26. Wentworth, H. A.: Variations of the normal blind spot with special reference to the formation of diagnostic scale. *Am. J. Ophthalmol.* 14:889, 1931.

27. Stürmer, J., Schroedel, C., and Rappl, W.: Low-background-brightness, static SLO fundus-perimetry. *ARVO abstracts. Supplement to Invest. Ophthalmol. Vis. Sci. Philadelphia, J. B. Lippincott*, 1990, p. 504.

Late Recovery of Function After Oculomotor Nerve Palsy

Karl C. Golnik, M.D., and Neil R. Miller, M.D.

We studied three patients who developed oculomotor nerve paresis from different causes. Each patient improved somewhat over several months, after which there was no further improvement for at least six months. Although the pareses were thought to be stable after the period of no improvement, each patient subsequently had further improvement in both motility and alignment with resolution of diplopia in primary position and in more than one of the cardinal positions of gaze. Patients with oculomotor nerve paresis may improve further after an initial period of improvement followed by several months of stability.

THE RATE OF RECOVERY of an oculomotor nerve paresis is related to both the cause and the severity of the paresis. Vasculopathic oculomotor nerve pareses, such as those in patients with diabetes mellitus or systemic hypertension, usually recover within a few months, whereas oculomotor nerve pareses caused by compression or trauma usually improve over a longer period of time. Most investigators believe that, regardless of the cause, recovery of an oculomotor nerve paresis is usually complete within one year after onset of the paresis or treatment of the responsible lesion and that surgery for persistent misalignment should be considered if there is no improvement after six to 12 months or once improvement stops.

We studied three patients with oculomotor nerve paresis from different causes who had late recovery of oculomotor function with resolution of diplopia in primary position and in

more than one of the cardinal positions of gaze. This occurred after a period of improvement followed by an apparent lack of improvement for several months. These observations suggest that the recovery of an oculomotor nerve paresis may not be constant but may follow an intermittent course, with improvement occurring after a lengthy period of stability.

Case Reports

Case 1

In April 1981, a 42-year-old man fell on a stick and sustained lacerations of his right lower eyelid and the inferior bulbar conjunctiva of his right eye. A computed tomographic scan showed no damage to the orbital floor. The lacerations were closed, and orbital exploration disclosed an intact inferior rectus muscle. Two months later, the patient was referred for neuro-ophthalmic examination because of persistent vertical diplopia.

Visual acuity was 20/20 in each eye, and color vision was normal. Visual fields performed by kinetic perimetry were full. There was no afferent pupillary defect. The lacerations were healed, the eye was white and quiet, and there was neither proptosis nor enophthalmos. There was, however, marked limitation of depression and mild limitation of adduction of the right eye. In primary position, at distance, there was a 25-prism diopter right hypertropia that increased to 48 prism diopters on downgaze and decreased to 3 prism diopters on upgaze (Table 1). The patient also had 7 degrees of subjective right incyclotorsion. Slit-lamp examination, intraocular pressure measurements, and ophthalmoscopic examination showed no abnormalities.

The patient underwent a repeat orthoptic examination six months later (eight months after the injury), at which time there was no significant change in either ocular alignment or motility (Table 1). It was thought that his strabismus was stable, and he was offered surgical treatment, which he declined. Three years after

Accepted for publication Jan. 17, 1991.

From the Wilmer Eye Institute, Johns Hopkins Hospital, Baltimore, Maryland. This study was presented at the Eighth Annual Marion Humphries Symposium, Sept. 23, 1990, University of Virginia Health Science Center, Charlottesville, Virginia.

Reprint requests to Neil R. Miller, M.D., Johns Hopkins Hospital, Wilmer Eye Institute, 600 N. Wolfe St., Maumenee Bldg., Rm. B-109, Baltimore, MD 21205.

TABLE 1
ORTHOPTIC MEASUREMENTS OF CASE 1*

	EXAMINATION DATE		
	JUNE 1981	DECEMBER 1981	APRIL 1984
Primary position	25 RHT	23 RHT	5 RH(T)
Upgaze	3 RHT	6 RHT	Orthophoria
Downgaze	48 RHT	48 RHT	2 RHT

*All measurements made with patient viewing a distant target. Measurements are in prism diopters. RHT indicates right hypertropia.

the injury, in April 1984, the patient noted resolution of double vision. He had an intermittent right hypertropia of only 5 prism diopters in primary position; he was orthophoric in upgaze; and he had a 2-prism diopter hypertropia in downgaze (Table 1).

Case 2

In 1983, a 48-year-old woman developed an acute, complete, right oculomotor nerve paresis. A computed tomographic scan disclosed evidence of a pituitary adenoma with associated hemorrhage, and the patient was treated with transsphenoidal removal of tumor, blood, and necrotic tissue. Postoperatively, the patient noted binocular oblique diplopia that completely resolved over three months. She then had no visual difficulties until three years later, when she developed the sudden onset of left blepharoptosis and recurrent binocular oblique diplopia. Magnetic resonance imaging disclosed recurrent tumor, and the patient was referred to the neuro-ophthalmology unit for examination.

Visual acuity was R.E.: 20/20 and L.E.: 20/25. Color vision using Hardy-Rand-Rittler pseudoisochromatic plates was R.E.: 10/10 and L.E.: 8.5/10. Pupil measurements were R.E.: 3 mm and L.E.: 8 mm. Neither pupil reacted to light or near stimulation. Kinetic perimetry disclosed a mild superotemporal depression in the visual field of the right eye and an inferonasal arcuate defect in the visual field of the left eye. The right eye had full ductions, but there was eyelid retraction on adduction. There was a complete left blepharoptosis, and the left eye was completely immobile (Table 2). Slit-lamp biomicroscopic examination and intraocular pressure measurements showed normal results. Ophthalmoscopy disclosed a normal right optic disk. The left disk was mildly pale.

Transsphenoidal removal of the recurrent pituitary tumor was performed in October 1986, after which the patient underwent radiation therapy (4,500 cG, 25 fractions over four weeks). In January 1987, two months after completion of radiation therapy, the mild left optic neuropathy persisted, but the anisocoria had diminished, and the left blepharoptosis had improved. The patient had a 20-prism diopter left hypotropia and 10-prism diopter exotropia. Ductions in the right eye remained full. Ductions had improved in the left eye but the left eye still did not elevate above the midline (Table 2). In July 1987, six months later, orthoptic measurements showed that abduction in the left eye had improved, but adduction, elevation, and depression were unchanged (Table 2).

The patient returned in March 1988, 16 months after completion of radiation therapy, at which time ductions in the left eye were unchanged (Table 2). The patient now had a 10-prism diopter left hypertropia. There was left eyelid retraction during both depression and adduction, and adduction occurred during attempted elevation, which indicated aberrant regeneration of the oculomotor nerve. In July 1990, four years after treatment, the patient stated that her double vision had resolved since her last visit. Indeed, the patient had no deviation in primary position, and abduction, adduction, and elevation had all improved (Table 2).

Case 3

In February 1988, a 54-year-old woman developed an acute right retrobulbar hemorrhage while undergoing bilateral intranasal ethmoidectomies and anastomies for treatment of chronic paranasal sinus disease. Intraocular pressure increased to 30 mm Hg in the right eye, and the eye became proptotic. A right lateral canthotomy was performed, a lateral rhinostomy incision was made, and the medial periorbita was elevated away from the medial orbital wall and incised. No definite site of hemorrhage was identified. Absorbable gelatin sponges and microfibrillar collagen were used for hemostasis. Postoperatively, the patient had a complete right blepharoptosis and had oblique diplopia when the right eyelid was elevated. One month later, magnetic resonance imaging showed no abnormalities in the right orbit. The patient was referred for neuro-ophthalmic examination four months after the operation because of persistent vertical diplopia.

At the time of initial examination, in June 1988, visual acuity was R.E.: 20/30 and L.E.:

TABLE 2
ORTHOPTIC MEASUREMENTS OF CASE 2*

	EXAMINATION DATE				
	AUGUST 1986	JANUARY 1987	JULY 1987	MARCH 1988	JULY 1990
Primary position alignment at distance (prism diopters)	—	20 LHPO 10 XT	15 LHPO 8 XT	10 LHT	Orthophoria
Left eye duction (degrees of excursion from midline)					
Adduction	0	28	30	30	40
Abduction	0	20	44	38	53
Elevation	0	0	0	2	13
Depression	0	45	30	30	30

*XT indicates exotropia; ET indicates esotropia; LHPO indicates left hypotropia; and LHT indicates left hypertropia.

20/20, and color vision using Hardy-Rand-Rittler plates was R.E.: 8.5/10 and L.E.: 9.5/10. Pupil measurements were 3 mm each, and there was no afferent pupillary defect. Visual fields performed by kinetic perimetry were full. There was no proptosis or enophthalmos, but there was 3 mm of right blepharoptosis. The patient had a 4-prism diopter right hypotropia in primary position. The hypotropia increased on upgaze and changed to a hypertropia on downgaze (Table 3). The left eye had limited adduction, elevation, and depression. Neither ocular motility nor alignment had changed at examination three months later in September 1988 (Table 3) or one year later in September 1989 (Table 3). In February 1990, however, the patient returned 24 months after the injury and stated that her double vision had recently resolved. The patient was orthophoric in primary position and in downgaze (Table 3), and movement of the right eye had improved markedly.

Discussion

Late improvement of oculomotor nerve palsy occurred in each of our three patients. The first patient sustained trauma to the right orbit and subsequently lost inferior rectus muscle function. The examination suggested injury of the oculomotor nerve branch to the inferior rectus muscle rather than injury to the muscle itself. Despite ocular motility and alignment that remained unchanged eight months after the injury, the patient's diplopia eventually resolved, and there was marked improvement in motility when he was reexamined three years later.

The second patient developed unilateral, complete ophthalmoplegia caused by recurrent

pituitary adenoma affecting the ocular motor nerves in the cavernous sinus. After transsphenoidal removal of the tumor followed by radiation therapy, there was initial improvement in motility. Abduction subsequently continued to improve, but adduction, elevation, and depression did not change over the next 16 months. Nevertheless, orthoptic examination four years later showed that diplopia had resolved and vertical ductions had improved substantially.

The third patient developed blepharoptosis and diplopia from oculomotor nerve dysfunction after paranasal sinus surgery complicated by retrobulbar hemorrhage. Initial improvement occurred over several weeks, but neither ocular motility nor alignment improved over the subsequent 15 months. Nevertheless, despite more than one year of stability, the patient's diplopia eventually resolved and her ocular motility significantly improved.

Oculomotor nerve dysfunction can result from many causes.¹ The most common causes are ischemia, trauma, and compression.²⁻⁴ Prognosis is related in part to the pathogenesis of the impairment.

An ischemic oculomotor nerve paresis is typically associated with return of function over several months.^{2,5} Recovery may occur faster when the pupil is not affected or when the paresis is incomplete.⁶ Duration of impairment thus may be dependent in part on extent of damage.

Resolution of traumatic oculomotor nerve palsy may not begin for weeks to months^{7,8} and may never be complete. Improvement in ocular motility and alignment after one year of stability is rare, although Krohel⁸ described one patient in whom improvement in blepharoptosis did not occur until one to two years after injury.

Compressive oculomotor nerve paresis is fre-

TABLE 3
ORTHOPTIC MEASUREMENTS OF CASE 3*

	EXAMINATION DATE			
	JUNE 1988	SEPTEMBER 1988	SEPTEMBER 1989	APRIL 1990
Primary position	4 RHPO	5 RHPO	6 RHPO	Orthophoria
Upgaze	20 RHPO	14 RHPO	20 RHPO	25 RHPO
Downgaze	9 RHT	10 RHT	9 RHT	Orthophoria

*All measurements made with patient viewing a distant target. Measurements are in prism diopters. RHT indicates right hyperopia and RHPO indicates right hypotropia.

quently caused by an intracranial aneurysm.⁹⁻¹¹ The extent of recovery after treatment of the aneurysm depends on both the severity of pre-operative dysfunction⁹ and the interval between onset and treatment.¹² Complete recovery usually does not occur if treatment is delayed more than two weeks after onset of the paresis.¹³ Most of the improvement occurs within three months, although recovery may continue for one year.¹²⁻¹⁵ Recovery after one year is uncommon; however, Grayson, Soni, and Spooner¹² described three patients who had only partial recovery at one year but who had no dysfunction at the five-year follow-up. Suzuki, Mizoi, and Sato¹⁶ described one patient who had improvement of blepharoptosis two years after treatment. It is not clear from these reports whether there was gradual improvement throughout the period of follow-up or if improvement occurred after a period of stability.

The mechanism of oculomotor nerve recovery is axonal regeneration. Bender and Fulton¹⁷ surgically transected oculomotor nerves in monkeys, which produced complete oculomotor nerve paralysis. The transected nerve ends were apposed, and return of oculomotor nerve function was observed five days later. There was no recovery in vertical movement during the six-month experiment. The authors thought that the poor vertical motility was not caused by lack of muscular function but rather by cocontraction of the vertical recti muscles produced by aberrant regeneration of axons. Similar axonal regeneration occurs in both cats and rats.^{18,19}

Axonal regrowth was presumably the mechanism of the early improvement in motility in our patients; however, it is difficult to under-

stand the subsequent period of stability after which there was further improvement. One would expect the rate of axonal regeneration to be relatively constant, but this hypothesis was not supported by the clinical course of our patients.

The frequency of late recovery of oculomotor nerve function is difficult to ascertain, since surgical intervention is usually undertaken within one year of the onset of nerve damage. Patients who either refuse surgery or are not surgical candidates may nevertheless have spontaneous improvement more than one year after the onset of oculomotor nerve paresis. We would not necessarily withhold surgery in those patients who have no recovery of oculomotor nerve function over the six- to 12-month period after the onset of the paresis or the treatment of its cause. It may be appropriate, however, to examine some patients who initially improve and then stabilize at regular intervals for several months before considering surgery or to treat such patients with nonsurgical procedures, such as intramuscular injection of botulinum A toxin.

References

1. Miller, N. R.: Walsh and Hoyt's Clinical Neuro-Ophthalmology, ed. 4, vol. 2. Baltimore, Williams & Wilkins, 1985, p. 676.
2. Rush, J. A., and Younge, B. R.: Paralysis of cranial nerves III, IV, and VI. *Arch. Ophthalmol.* 99:76, 1981.
3. Rucker, C. W.: Paralysis of the third, fourth, and sixth cranial nerves. *Am. J. Ophthalmol.* 46:787, 1958.
4. —: The causes of paralysis of the third, fourth, and sixth cranial nerves. *Am. J. Ophthalmol.* 61:1293, 1966.
5. Green, W. R., Hackett, E. R., and Schlezinger, N. S.: Neuro-ophthalmologic evaluation of oculomotor nerve paralysis. *Arch. Ophthalmol.* 72:154, 1964.
6. Naghmi, R., and Subuhi, R.: Diabetic oculomotor mononeuropathy. Involvement of pupillomotor fibers with slow resolution. *Horm. Metab. Res.* 22:38, 1990.
7. Falbe-Hansen, I., and Gregerson, E.: Prognosis for disturbance of ocular motility following trauma to the head. *Acta Ophthalmol.* 37:359, 1959.
8. Krohel, G. B.: Blepharoptosis after traumatic third-nerve palsies. *Am. J. Ophthalmol.* 88:598, 1979.
9. Cantu, R. C., Souders, T., and Hepler, R. S.: Effects of carotid ligation on aneurysm-induced oculomotor palsy. *J. Neurosurg.* 31:528, 1969.

10. Hepler, R. S., and Cantu, R. C.: Aneurysms and third nerve palsies. *Arch. Ophthalmol.* 77:604, 1967.
11. Raja, I. A.: Aneurysm-induced third nerve palsy. *J. Neurosurg.* 36:548, 1972.
12. Grayson, M. C., Soni, S. R., and Spooner, V. A.: Analysis of the recovery of third nerve function after direct surgical intervention for posterior communicating artery aneurysms. *Br. J. Ophthalmol.* 58:118, 1974.
13. Botterell, E. H., Lloyd, L. A., and Hoffman, H. J.: Oculomotor nerve palsy due to supraclinoid internal carotid artery berry aneurysm. *Am. J. Ophthalmol.* 54:609, 1962.
14. Soni, S. R.: Aneurysms of the posterior communicating artery and oculomotor paresis. *J. Neurol. Neurosurg. Psychiatry* 37:475, 1974.
15. Shenkin, H. A., Polakoff, P., and Finneson, B. E.: Intracranial internal carotid artery aneurysms. Results of treatment by cervical carotid artery ligation. *J. Neurosurg.* 15:183, 1958.
16. Suzuki, J., Mizoi, K., and Sato, T.: Disturbances of ocular motility due to cerebral aneurysm. Based upon the experience in 1000 directly operated patients. In Sammi, M., and Janetta, P. J. (eds.): *The Cranial Nerves*. Berlin, Springer Verlag, 1981, pp. 229-236.
17. Bender, M. B., and Fulton, J. F.: Factors in functional recovery following section of the oculomotor nerve in monkeys. *J. Neurol. Psychiatry* 2:285, 1939.
18. Sibony, P. A., Evinger, C., and Lessell, S.: Retrograde horseradish peroxidase transport after oculomotor nerve injury. *Invest. Ophthalmol. Vis. Sci.* 27:975, 1986.
19. Fernandez, E., Pallini, R., Gangitano, C., Del Fa, A., Sangiacomo, C. O., Talamont, G., Draicchio, F., and Sbriccoli, A.: Oculomotor nerve regeneration in rats. *J. Neurosurg.* 67:428, 1987.

OPHTHALMIC MINIATURE

The Spanish Gypsies preserve the characteristic eye. The form is perfect, and it has an especial look to which is attributed the power of engendering grandes passions—one of the privileges of the eye. I have often remarked on its fixity and brilliance, which flashes like phosphoric light, the gleam which in some eyes denotes madness. I have also noted the "far-off" look which seems to gaze at something beyond you, and the alternation from the fixed stare to a glazing or filming over of the pupil.

Edward Rice, *Captain Sir Richard Francis Burton*
New York, Macmillan Publishing Company, 1990, p. 122

Squamous Cell Carcinoma of the Cornea

James A. Cameron, M.D., and Ahmed A. Hidayat, M.D.

We treated two patients with primary squamous cell carcinoma of the cornea without involvement of the corneoscleral limbus. Superficial keratectomy and cryotherapy in one patient and penetrating keratoplasty in the other patient resulted in no recurrence of the tumor after 46 and nine months, respectively. Actinic damage and late manifestation caused by poor vision in both eyes of both patients may have been the risk factors for development of this tumor.

SQUAMOUS CELL CARCINOMA involving the cornea has been described in association with an adjacent limbal lesion.¹⁻³ We treated two patients with primary squamous cell carcinoma of the cornea without limbal involvement.

Case Reports

Case 1

In November 1983, a 40-year-old man came to the emergency room with pain in the left eye and a blood-tinged discharge of three weeks' duration. Vision had been poor in both eyes from childhood, and the right eye was completely blind since childhood. Vision had deteriorated gradually in the left eye during the preceding three years. The patient had had no previous ocular surgery, and systemically he was in good health.

On examination, visual acuity was R.E.: no light perception and L.E.: light perception with poor projection. A large-amplitude horizontal

nystagmus was present in both eyes. The horizontal corneal diameters were R.E.: 13 mm and L.E.: 15 mm.

The right eye was phthisic, and the left globe was buphthalmic. Tactile intraocular pressure was normal in the left eye. An elevated, central corneal lesion measuring 10 mm in width and 8 mm in height was present on the left cornea (Fig. 1). Large, superficial blood vessels were present at the 12, 5, and 8 o'clock meridians on the cornea. There was no involvement of the peripheral cornea or corneoscleral limbus.

On Nov. 30, 1983, a superficial keratectomy was performed followed by a double, freeze-thaw cryotherapy with a freeze phase of two to three seconds. Cryotherapy was applied to the base and the margins of the lesions to include approximately 1 mm of apparently normal corneal epithelium.

Histopathologically, the corneal epithelium was replaced by sheets and nests of atypical squamous cells that had invaded superficially the chronically inflamed stroma, consistent with microinvasive carcinoma. The deeper neoplastic cells showed more cellular atypia, with pleomorphic nuclei and prominent nucleoli (Fig. 2). Hyperkeratosis, parakeratosis, and less cellular atypia were characteristic of the superficially located cells. The lines of surgical transection were free of tumor cells.

The patient was last examined in September 1987, 46 months after the initial manifestation. At that time, there was no recurrence of the lesion and no staining of the conjunctiva or cornea with rose bengal dye.

Case 2

In June 1989, a 57-year-old man came to the emergency room with poor vision in the left eye and a white spot on the cornea that had been present for one year. Vision in the right eye had been poor for at least two to three years before coming to the emergency room. The patient had had no previous ocular surgery, and systemically he was in good health.

On examination, visual acuity was R.E.: 20/

Accepted for publication Feb. 1, 1991.

From the King Khaled Eye Specialist Hospital, Riyadh, Saudi Arabia (Dr. Cameron), and Department of Ophthalmic Pathology, Armed Forces Institute of Pathology, Washington, D.C. (Dr. Hidayat).

Reprint requests to James A. Cameron, M.D., King Khaled Eye Specialist Hospital, P.O. Box 7191, Riyadh 11462, Saudi Arabia.

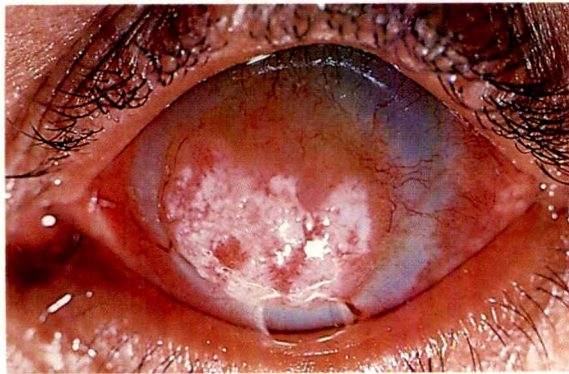


Fig. 1 (Cameron and Hidayat). Case 1. Central, elevated corneal tumor with large superficial blood vessels at the 12, 5, and 8 o'clock meridians on the cornea. Whitened surface (leukoplakia) of the tumor is caused by keratinization.

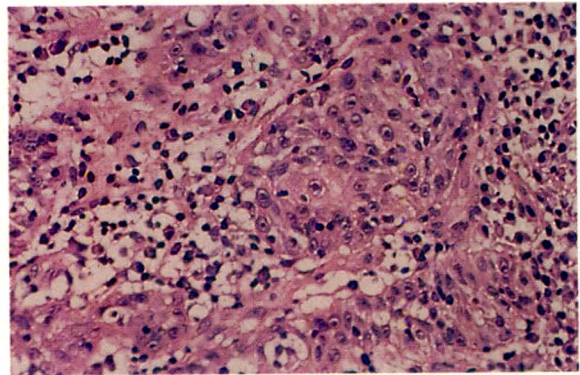


Fig. 2 (Cameron and Hidayat). Case 1. The deeper portion of the tumor shows stromal invasion by atypical squamous cells with eosinophilic cytoplasm, pleomorphic nuclei, and prominent nucleoli. Lymphocytes and plasma cells surround the neoplastic cells (hematoxylin and eosin, $\times 300$).

300 and L.E.: hand motions. Climatic droplet keratopathy (elastotic degeneration) with corneal scarring and advanced immature cataracts were noted in both eyes. Intraocular pressure was 20 mm Hg in both eyes by pneumotonometry. Ultrasound examination disclosed abnormal optic nerve cupping in both eyes.

An elevated, white bilobed lesion was present on the central cornea of the left eye (Fig. 3). Rose bengal dye stained most of the lesion with no adjacent corneal or conjunctival staining. Large, superficial blood vessels were present at the 6, 8, and 11 o'clock meridians on the cornea.

In August 1989, a penetrating keratoplasty with extracapsular cataract extraction and posterior chamber intraocular lens implantation was performed in the left eye.

On histopathologic examination, the corneal epithelium showed an abrupt change from normal to abnormal. Acanthosis, hyperkeratosis, parakeratosis, and loss of polarity were present. Nuclear atypia was more evident in the deeper layers of the tumor. These features resembled the hypertrophic type of actinic keratosis except for the presence of irregular masses of squamous cells that had proliferated downward and invaded the corneal stroma superficially, near the central portion of the tumor (Fig. 4). The deep portion of the neoplasm showed a horn pearl, which consisted of a concentric layer of squamous cells with increasing keratinization toward the center (Fig. 4). The superficial, scarred stroma had rare deposits of homogeneous material consistent with elastotic degeneration (climatic droplet keratopathy). Multiple sections at different levels

showed normal corneal epithelium at the periphery of the specimen.

Nine months after the operation, there was no recurrence of the lesion or any staining of the conjunctiva or cornea with rose bengal dye. Best-corrected visual acuity was 20/160, limited by endstage glaucomatous optic nerve cupping.

Discussion

Pizzarello and Jakobiec⁴ used the term conjunctival intraepithelial neoplasia to describe the spectrum of epithelial changes ranging from mild dysplasia to carcinoma in situ. Corneal intraepithelial neoplasia refers to the same spectrum as it pertains to the corneal epithelium.⁵ Squamous cell carcinoma is diagnosed when the dysplastic process breaks through the epithelial basement membrane into the substantia propria of the conjunctiva or through the basement membrane into Bowman's layer and stroma of the cornea.

Corneal intraepithelial neoplasia is characterized by a minimally elevated, gray plaque on the cornea. There is usually a distinctive, fibrillated margin consisting of sharply demarcated, finger-shaped extensions as well as isolated islands. There is usually an associated limbal lesion, although isolated corneal intraepithelial neoplasia without any other associated ocular abnormality has been described.^{2,5-11} Previous authors have speculated that isolated corneal intraepithelial neoplasia may be a precursor to



Fig. 3 (Cameron and Hidayat). Case 2. Central bilobed, white, elevated lesion on the central cornea.

primary carcinoma of the cornea, just as conjunctival intraepithelial neoplasia is thought to be a precursor of squamous cell carcinoma of the conjunctiva.⁴⁻⁷ Brown and associates¹¹ described a patient with an elevated, gray-white, corneal lesion that on histopathologic examination was found to be corneal intraepithelial neoplasia with marked hyperkeratosis.

The findings in our two patients further extend the spectrum of corneal epithelial neoplasia. Both patients had large, elevated, central corneal lesions that on histopathologic examination showed microinvasive, well-differentiated, squamous cell carcinoma. Chronic inflammatory cells were present in the cornea of both patients. Despite the relatively large size of both corneal tumors and the history of a white, corneal lesion noted for at least one year in one patient, there was only invasion into the superficial corneal stroma in both patients. The compact lamellar architecture of the cornea probably acted as at least a partial barrier to limit tumor spread into the eye.

Almost all dysplastic lesions involving the conjunctiva or cornea also involve the corneoscleral limbus. Just as early dysplasia of the uterine cervix develops almost without exception at the squamous-columnar junction,¹² so too with dysplastic lesions of the eye, which occur at the transition from conjunctival to corneal epithelium. This is thought to be caused by the increased mitotic activity in this area. Although in our two cases there was no involvement of the corneoscleral limbus, it is possible that the original abnormal cells may have had their origin at the corneoscleral limbus and subsequently became neoplastic after migration to the central cornea. This may explain previously reported cases of isolated corneal intraepithelial neoplasia and also our two



Fig. 4 (Cameron and Hidayat). Case 2. Acanthosis, hyperkeratosis, and parakeratosis of the corneal epithelium. Irregular masses of atypical squamous cells proliferate downward and invade the corneal stroma superficially. The deep portion of the neoplasm shows a horn pearl composed of concentric layers of squamous cells with increasing keratinization toward the center (hematoxylin and eosin, $\times 75$).

cases of squamous cell carcinoma of the cornea without limbal involvement. Lemp and Mathers¹³ supported the theory that the corneoscleral limbus is the major source of epithelial cell regeneration in the normal cornea and that there is normally a centripetal movement of epithelial cells. The pattern of epithelial iron lines, the central movement of epithelial white dots between sutures after penetrating keratoplasty,¹⁴ and the vortex pattern in the corneal epithelium in many clinical conditions¹⁵ all support the theory of a centripetal sliding of cells from the corneoscleral limbus to the center of the cornea.

Treatment in our patients consisted of superficial keratectomy and freeze-thaw cryotherapy in one patient and penetrating keratoplasty in the other patient. In the management of conjunctival intraepithelial tumors and squamous cell carcinoma, the combination of excision with superficial freezing resulted in a recurrence rate less than that with excision or freezing alone.¹⁶ In the second patient, a penetrating keratoplasty was performed to remove the localized tumor mass and to improve vision. Rose bengal 1% is helpful in delineating the abnormal epithelial cells before surgical treatment.¹⁷ There has been no recurrence of either lesion or abnormal epithelial staining in both patients with a follow-up period of 46 and nine months, respectively. Conjunctival hyperemia regressed in both patients after removal of the corneal tumor.

Ultraviolet light is thought to be the major etiologic factor in squamous cell carcinoma of

the conjunctiva.¹⁸ It also probably plays a major role in the development of primary squamous cell carcinoma of the cornea. Both tumors showed suggestions of actinic damage as manifested by hyperkeratosis and parakeratosis at the surface and more cellular atypia in the deeper layers. Climatic droplet keratopathy, frequently related to sun damage, was found in the cornea of the second patient. In our first patient, the left eye was probably more at risk from ultraviolet damage resulting from the buphthalmic globe. Poor vision in both eyes of both patients from other causes resulting in a delay in manifestation may also have been a risk factor for the development of this tumor. Late manifestation may have been a contributing factor in the lesion progressing from actinic keratosis to microinvasive squamous cell carcinoma.

References

1. Daxecker, F., Philipp, W., and Mikuz, G.: Corneal carcinoma. *Ophthalmologica* 198:163, 1989.
2. Erie, J. C., Campbell, R. J., and Liesegang, T. J.: Conjunctival and corneal intraepithelial and invasive neoplasia. *Ophthalmology* 93:176, 1986.
3. Freedman, J., and Röhm, G.: Surgical management and histopathology of invasive tumors of the cornea. *Br. J. Ophthalmol.* 63:632, 1979.
4. Pizzarello, L. D., and Jakobiec, F. A.: Bowen's disease of the conjunctiva. A misnomer. In Jakobiec, F. A. (ed.): *Ocular and Adnexal Tumors*. Birmingham, Aesculapius, 1978, pp. 553-571.
5. Waring, G. O., III, Roth, A. M., and Ekins, M. B.: Clinical and pathologic description of 17 cases of corneal intraepithelial neoplasia. *Am. J. Ophthalmol.* 97:547, 1984.
6. Campbell, R. J., and Bourne, W. M.: Unilateral central corneal epithelial dysplasia. *Ophthalmology* 88:1231, 1981.
7. Roberson, M. C.: Corneal epithelial dysplasia. *Ann. Ophthalmol.* 16:1147, 1984.
8. Geggel, H. S., Friend, J., and Boruchoff, A.: Corneal epithelial dysplasia. *Ann. Ophthalmol.* 17:27, 1985.
9. Dark, A. J., and Streeten, B. W.: Preinvasive carcinoma of the cornea and conjunctiva. *Br. J. Ophthalmol.* 64:506, 1980.
10. Cruess, A. F., Wasan, S. M., and Willis, W. E.: Corneal epithelial dysplasia and carcinoma in situ. *Can. J. Ophthalmol.* 16:171, 1981.
11. Brown, H. H., Glasgow, B. J., Holland, G. N., and Foos, R. Y.: Keratinizing corneal intraepithelial neoplasia. *Cornea* 8:220, 1989.
12. Goodman, H. M., Griffiths, C. T., and Knapp, R. C.: The cervix. In Kistner, R. W. (ed.): *Gynecology. Principles and Practice*, ed. 4, chap. 4. Chicago, Year Book Medical Publishers, 1986, pp. 97-148.
13. Lemp, M. A., and Mathers, W. D.: Corneal epithelial cell movement in humans. *Eye* 3:438, 1989.
14. Kaye, D. B.: Epithelial response in penetrating keratoplasty. *Am. J. Ophthalmol.* 89:381, 1980.
15. Bron, A. J.: Vortex patterns of the corneal epithelium. *Trans. Ophthalmol. Soc. U.K.* 93:455, 1973.
16. Fraunfelder, F. T., and Wingfield, D.: Management of intraepithelial conjunctival tumors and squamous cell carcinomas. *Am. J. Ophthalmol.* 95:359, 1983.
17. Wilson, F. M., II: Rose bengal staining of epibulbar squamous neoplasms. *Ophthalmic Surg.* 7:21, 1976.
18. Clear, A. S., Chirambo, M. C., and Hutt, M. S. R.: Solar keratosis, pterygium, and squamous cell carcinoma of the conjunctiva in Malawi. *Br. J. Ophthalmol.* 63:102, 1979.

Varicella Disciform Stromal Keratitis

Kirk R. Wilhelmus, M.D., M. Bowes Hamill, M.D., and Dan B. Jones, M.D.

We treated five patients, aged 26, 4, 6, 13, and 7 years, who developed disciform stromal keratitis one, four, four, eight, and ten weeks, respectively, after the onset of the acute vesicular exanthema. Serologic testing confirmed recent varicella and excluded other infectious causes in two cases. After initial improvement with a topical corticosteroid, three patients developed recurrent corneal inflammation resembling zoster keratitis. These cases and previous reports indicate that varicella-zoster virus is a cause of disciform stromal keratitis that may occur and recur several weeks or months after the primary skin rash has resolved.

CHICKENPOX is a diffuse vesicular skin rash, mainly affecting children, caused by primary infection with varicella-zoster virus.¹ The resemblance of the cutaneous lesions to chickpeas probably gave rise to the term chickenpox to emphasize its mildness and similarity to smallpox, and its synonym varicella originated as a diminutive form of variola. The eye may be affected during, after, or rarely before the exanthema. Among the possible ocular complications of chickenpox are keratoconjunctivitis, uveitis, and neuro-ophthalmic changes.²⁻⁵

Few studies have determined the frequency or incidence of various ocular findings in patients with chickenpox. Over a one-year interval, Griffin and Searle⁶ found five of 125 children (4%) with varicella who had conjunctivitis, one with a limbal lesion. In a two-year period, Kachmer, Annable, and DiMarco⁷ identified 33 of 82 children (40%) with chickenpox who had ocular or eyelid involvement, including six (7%) with eyelid lesions, ten (12%) with punctate keratopathy, and 21 (26%) with iritis.

Of 24 children referred because of ocular symptoms, Jordan, Noel, and Clarke⁸ reported eyelid pocks and conjunctivitis as the most common findings, followed by uveitis and keratitis. We treated five patients with disciform stromal keratitis after chickenpox.

Case Reports

Case 1

A 26-year-old woman was examined for decreased vision and redness of the left eye. Without known contact with a rash illness, she had developed fever seven days previously, followed two days later by vesicular dermatitis beginning in the neck region with subsequent spread to the face, trunk, arms, and legs without localized involvement. Initial ocular signs and symptoms included left upper eyelid edema, photophobia, and decreased vision. Slit-lamp biomicroscopy disclosed faint, patchy anterior stromal opacities with central disciform stromal edema, fine cellular infiltration, and pseudo cornea guttata. The anterior chamber contained trace flare and rare cells.

Treatment was begun with prednisolone acetate 1% five times daily and scopolamine hydrochloride 0.5% three times daily. Improvement occurred within two days, and a tapering dose of topical corticosteroid was continued. Within ten days, visual acuity improved to 20/20 with resolution of the stromal keratitis, which left a faint residual anterior stromal haze.

Case 2

A 4-year-old girl was referred for stromal keratitis four weeks after chickenpox. Mild conjunctival hyperemia with pseudoblepharoptosis of the left eye had developed over the preceding ten days and had not responded to topical erythromycin ointment. Visual acuity was R.E.: 20/20 and L.E.: 20/400. Slit-lamp examination showed a well-demarcated disciform stromal keratitis with localized edema, pseudo cornea guttata, and mild iritis. Serolog-

Accepted for publication Feb. 6, 1991.

From the Department of Ophthalmology, Cullen Eye Institute, Baylor College of Medicine, Houston, Texas.

Reprint requests to Kirk R. Wilhelmus, M.D., One Baylor Plaza, Houston, TX 77030.

ic testing confirmed recent varicella and excluded other causes of stromal keratitis. Four weeks after onset of the skin rash, varicella-zoster virus IgG was 1:16, herpes simplex IgM and IgG were not detectable ($< 1:10$), and Epstein-Barr viral capsid and nuclear IgGs were not detectable. Six weeks later, the herpes simplex antibodies were still not detectable. The microhemagglutination assay for *Treponema pallidum* was nonreactive.

Topical prednisolone acetate 1% was begun four times daily. The patient improved over the next ten days with reduced stromal edema and infiltration, and visual acuity improved to 20/30. The topical corticosteroid was gradually tapered over the subsequent four weeks, but increased corneal inflammation with iritis occurred when it was being administered once daily. As the topical corticosteroid dosage was subsequently reduced, increased central disciform edema again recurred. Peripheral superficial stromal vascularization and central scarring ensued and limited spectacle-corrected visual acuity to 20/60, which improved to 20/20 with contact lens correction. Chronic corticosteroid-dependent stromal keratouveitis resulted in prolonged use of daily prednisolone acetate 0.12% over the next four years.

Case 3

A 6-year-old girl developed sore throat, low-grade fever, and diffuse cutaneous lesions over her entire body including her face and periocular region. Her 4-year-old sister had recently had a similar skin rash during a chickenpox outbreak at the day care center. Ocular symptoms of photophobia and blurred vision began one month after the cutaneous lesions. Visual acuity was 20/40 in the affected eye because of central edema, diffuse stromal infiltration, and dendritic epithelial keratitis.

Treatment was begun with trifluridine 1% and tobramycin 0.3%. Because of increasing stromal edema with visual acuity of 20/60, we changed treatment to dexamethasone 0.1%. Despite initial improvement, recurrent stromal keratitis occurred during the subsequent year whenever the topical corticosteroid was tapered. Residual corneal scarring limited visual acuity to 20/30.

Case 4

A 13-year-old girl developed chickenpox; two neighborhood children also developed chickenpox, one immediately preceding the patient and one simultaneously. Eight weeks lat-

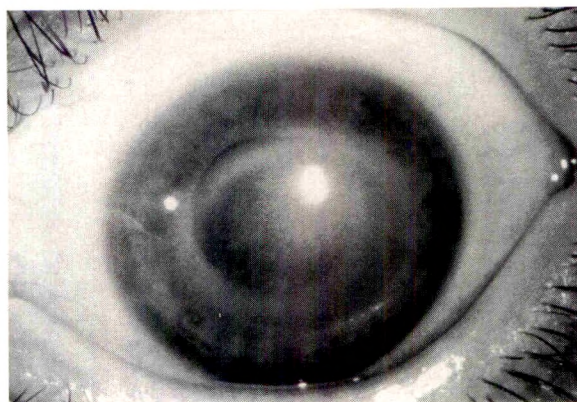


Figure (Wilhelmus, Hamill, and Jones). Case 4. Central disciform stromal keratitis occurring in a 13-year-old girl eight weeks after varicella.

er, well after all skin lesions had healed, the patient developed a red left eye. Initial treatment by her pediatrician with neomycin-polymyxin B-bacitracin ointment did not help. Ocular examination showed central nonnecrotizing disciform stromal keratitis with keratic precipitates and mild iritis (Figure). Serologic testing confirmed recent varicella and excluded other possible causes of stromal keratitis. Varicella-zoster virus antibody titers were tested 11 weeks after onset of the skin rash; IgM was 1:40, and IgG was 1:2,560. Seven weeks later, IgM was not detectable ($< 1:20$), and IgG was 1:640. Other serologic tests performed at eight or 11 weeks after the skin rash were as follows: herpes simplex IgM not detectable ($< 1:10$); herpes simplex IgG not detectable ($< 1:8$); Epstein-Barr viral capsid IgG not detectable ($< 1:10$); Epstein-Barr viral nuclear IgG not detectable ($< 1:4$); adenovirus IgG not detectable ($< 1:8$); mumps IgM not detectable; mumps IgG weakly positive (index = 1:3); mumps S antibody not detectable ($< 1:8$); mumps V antibody not detectable ($< 1:8$); rubella IgG not detectable; rubella IgM not detectable; rubella IgG positive (index = 1:4); rapid plasma reagin nonreactive; microhemagglutination assay for *T. pallidum* nonreactive; Lyme disease IgM not detectable; and Lyme disease IgG not detectable.

Topical prednisolone phosphate 1% was begun every two hours with initial improvement in visual acuity from 20/100 to 20/25. The patient subsequently developed corneal anesthesia with dendriform mucous plaques. Topical corticosteroids were gradually tapered, but she continued to develop recurrent stromal keratitis during the next year, which required pro-

longed corticosteroid therapy. Visual acuity remained limited to 20/40 because of residual stromal opacification and neurotrophic epithelial changes.

Case 5

A 7-year-old girl developed a red left eye ten weeks after chickenpox. Central disciform stromal keratitis was noted, and initial treatment included prednisolone acetate 1% every two hours and cyclopentolate hydrochloride 1% twice daily. Visual acuity worsened to 20/200 in the left eye because of a well-demarcated area of dense stromal edema with endothelial pseudo cornea guttata. Laboratory testing three months after the skin rash showed a nondetectable herpes simplex virus type 1 IgG ($< 1:10$) and a varicella-zoster virus IgG titer of 1:16.

After a four-week course of topical corticosteroid therapy, visual acuity gradually improved to 20/25 in the left eye with a faint residual opacity.

Discussion

Viremia and the typical mucocutaneous exanthema of varicella begin approximately two weeks after contact with an infected person. Self-limiting papules may appear in the mouth, pharynx, larynx, trachea, and gastrointestinal tract. Common ocular findings are eyelid vesicles or marginal erosions, acute conjunctivitis, and lesions resembling phlyctenules of the bulbar conjunctiva and semilunar fold. Humoral and cellular immunity control viral replication with spontaneous resolution of the skin and mucous membrane rash.

Corneal changes are infrequent but can occur during the first week or two after the onset of chickenpox. Punctate epithelial keratitis has been described infrequently.⁹ More commonly noted is an acute, pustular subepithelial infiltrate at the corneoscleral limbus.^{6,7,10-18} Epithelial erosion and ulceration contribute to the painful symptoms. A residual patch of peripheral corneal scarring with vascularization can remain.

Besides these focal, usually unilateral limbal infiltrates, a central superficial infiltrate with epithelial erosion can also occur.¹⁹⁻²⁶ Faint subepithelial opacification occurs after spontaneous healing, although extensive corneal scarring in early childhood has led to deprivation amblyopia.²⁷ Rarely, progressive necrotizing in-

flammation and iridocyclitis have progressed to corneal perforation and phthisis bulbi.²⁸

Nonnecrotizing, disciform stromal keratitis is an unusual complication of varicella.²⁻⁴ Clinical features include interstitial haze caused by localized edema and cellular infiltration. A discoid pattern of noncoalescent inflammatory cells is outlined by a slightly denser annular border. Mild iritis, grouped keratic precipitates, and endothelial pseudo cornea guttata are accompanying features.

Disciform keratitis after varicella has been diagnosed previously with no gender predilection, mainly in children (Table).^{3,29-48} All cases have been unilateral and equally distributed between right and left eyes. These reports emphasize the delayed onset of disciform keratitis, typically beginning several weeks after the initial skin rash.

Some of the reported cases of varicella stromal keratitis developed dendritic epithelial keratitis, characterized by gray, swollen epithelial cells in a nonulcerated, linear pattern similar to varicella-zoster virus dendrites. We also identified dendritic epithelial keratitis in one patient and dendriform mucous plaques and filaments resembling postvaricella-zoster neurotrophic keratitis in another. Even though viral antigen and intracellular viral inclusions can be found in the corneal epithelium,^{42,44} antiviral therapy is not apparently required for resolution.

Recurrent stromal keratitis prolongs the clinical course for months or even years. Despite initial antiinflammatory control with topical corticosteroid therapy, some patients develop subsequent corneal inflammation during gradual corticosteroid dosage reduction. Stromal keratitis with residual corneal scarring, sometimes leading to corneal transplantation,^{26,45} is the principal reason for visual loss. Other complications of varicella disciform keratitis include neurotrophic keratopathy,⁴⁹ iridocyclitis with secondary glaucoma,⁴¹ and iris stromal atrophy.³²

Because there are few distinguishing features among the various causes of disciform stromal keratitis, herpes simplex and other infectious causes must be considered. Serologic evaluation should exclude herpes simplex before concluding that recent varicella is causative rather than coincidental. For example, we have treated other patients with idiopathic stromal keratitis occurring a few weeks or months after varicella but could not establish a definite connection because of antibodies showing previous exposure to herpes simplex virus.

TABLE
DATA ON 32 REPORTED CASES OF VARICELLA DISCIFORM STROMAL KERATITIS*

STUDY	CASE NO., AGE (YRS), SEX, EYE	ONSET AFTER SKIN RASH	CORTICOSTEROID USE	COMPLICATIONS	VISUAL OUTCOME
Grüter ²⁹	1, NA, NA, NA	NA	No	NA	NA
	2, NA, NA, NA	NA	No	NA	NA
Pickard ³⁰	3, 10, M, R	3 weeks	No	None	20/15
Gözcü ³¹	4, NA, NA, NA	NA	No	NA	NA
Lowenstein ³²	5, 4, M, R	10 days	No	None	NA
Paufigue, Chauviré, and Barut ³³ and Paufigue and Bonamour ^{34, 35}	6, 5, M, R	3 weeks	No	NA	NA
	7, 4, F, R	3 weeks	No	NA	NA
	8, 7, F, L	NA	No	NA	NA
Neame ³⁶	9, 30, M, R	8 weeks	No	None	20/40
Cavara ³⁷	10, 8, NA, R	NA	No	NA	NA
Frandsen ³⁸	11, 8, F, L	3 weeks	No	None	20/80
	12, 5, M, R	3 weeks	No	None	20/40
Cavara ³⁹	13, 7, F, NA	NA	No	NA	NA
Moulié and Gofanovich Baron ⁴⁰	14, 9, M, R	8 days	No	None	20/20
Thygeson, Hogan, and Kimura ⁴¹	15, NA, NA, NA	NA	NA	Secondary glaucoma	NA
Gaud ³	16, NA, NA, R	NA	NA	NA	NA
Nesburn and associates ⁴²	17, 8, F, L	12 weeks	Yes	Dendritic keratitis, recurrent stromal keratitis	20/30
	18, 11, M, R	2 weeks	No	Dendritic keratitis	20/20
	19, 7, M, R	5 weeks	Yes	Dendritic keratitis, recurrent stromal keratitis	20/20
Tessler and Krimmer ⁴³ Uchida, Kaneko, and Hayashi ⁴⁴	20, 3, F, L	13 weeks	Yes	Dendritic keratitis, recurrent stromal keratitis	20/50
	21, 3, M, R	NA	Yes	Recurrent stromal keratitis, corneal graft rejection	NA
	22, 9, M, R	4 weeks	No	None	20/25
Wilson ⁴⁶ Uchida ⁴⁷	23, 6, F, L	10 weeks	Yes	Dendritic keratitis	NA
	24, 3, F, R	10 weeks	NA	Dendritic keratitis	NA
	25, 7, M, L	5 weeks	NA	Punctate epithelial keratitis	NA
deFreitas and associates ⁴⁸	26, 6, F, NA	6 weeks	Yes	Dendritic keratitis	20/25
	27, 10, M, NA	8 weeks	Yes	Dendritic keratitis	20/20
Present series (Wilhelmus, Hamill, and Jones)	28, 26, F, L	1 week	Yes	None	20/20
	29, 4, F, L	4 weeks	Yes	Recurrent stromal keratitis	20/20
	30, 6, F, L	4 weeks	Yes	Dendritic keratitis, recurrent stromal keratitis	20/30
	31, 13, F, L	8 weeks	Yes	Recurrent stromal keratitis, neuro- trophic keratopathy	20/40
	32, 7, F, L	10 weeks	Yes	None	20/25

*NA indicates not available.

Increased IgM or increasing IgG titers can assist in the diagnosis of varicella. Heterologous crossreactions are excluded if antiherpes simplex antibodies are not detected. Other causes of nonsuppurative stromal keratitis can be investigated with specific serologic tests for Epstein-Barr virus, mumps, syphilis, and Lyme disease.

The pathogenesis of varicella keratitis is unclear. As opposed to the limbal infiltrates that occur during or soon after the skin rash, the delayed onset of disciform stromal keratitis suggests an immunologic rather than infective reaction.³⁸ Perhaps viral antigen gains access to the corneal stroma or endothelium from preceding epithelial infection or through limbal or aqueous routes during viremia. In a human subject, topical inoculation of chickenpox vesicular fluid to a blind eye produced keratouveitis ten days later, but no inflammation occurred after subsequent rechallenge.²⁹ How viral and host factors interplay to produce stromal keratitis has not been determined. Because of the restraints of human experimentation, the sparse histopathologic material, and the limitations of animal models of varicella keratitis, further insights remain speculative.

The role of topical corticosteroid therapy for viral stromal keratitis remains controversial. We administered a topical corticosteroid to our patients with varicella disciform stromal keratitis because of persistent or progressive corneal inflammation and edema. Apparent rapid improvement was subsequently complicated by prolonged or recrudescing corneal inflammation in three of these five cases. Although topical corticosteroids can affect varicella keratitis and possibly predispose to occurrences,⁵⁰ we could not determine whether topical corticosteroids prolonged the duration or benefited visual outcome. Systemic corticosteroids are avoided because of possible dissemination.

The value of antiviral agents in the treatment of varicella ocular disease has not been determined. At the present time, we do not use topical antiviral prophylaxis during topical corticosteroid therapy for varicella stromal keratitis. Although oral acyclovir reduces the duration of viral shedding and fosters resolution of skin lesions during varicella, systemic antiviral agents have not been assessed for varicella corneal disease.

These cases of disciform stromal keratitis show that varicella is a cause of stromal keratitis. Because the signs of varicella can be limited to a mild skin rash several weeks or months

before corneal changes occur, diagnosis may be problematic. Clinical awareness of varicella keratitis is needed for appropriate evaluation of this potentially sight-limiting disease.

ACKNOWLEDGMENT

Frank R. Keith, Jr., M.D., Larry H. Taber, M.D., Paul J. Azar, Jr., M.D., Gerald M. Sheldon, M.D., and Ronald A. Schachar, M.D., referred the respective patients for this study.

References

1. Liesegang, T. J.: The varicella-zoster virus. Systemic and ocular features. *J. Am. Acad. Dermatol.* 11:165, 1984.
2. Bonamour, G.: Les manifestations oculaires des maladies infectieuses éruptives de l'enfance. *J. Med. Lyon* 34:557, 1953.
3. Gaud, F.: Les complications oculaires des maladies infectieuses éruptives de l'enfance. *Arch. Ophthalmol.* 18:25, 1958.
4. Bonamour, G., and Gaillot, J.: Les complications oculaires de la varicelle. *J. Med. Lyon* 40:663, 1959.
5. Nataf, R., Lépine, P., and Bonamour, G.: Oeil et Virus. *Viroses Oculaires Manifestations Ophtalmologiques des Maladies Générales à Virus*. Paris, Masson, 1960, p. 577.
6. Griffin, W. P., and Searle, C. W. A.: Ocular manifestations of varicella. *Lancet* 2:168, 1953.
7. Kachmer, M. L., Annable, W. L., and DiMarco, M.: Iritis in children with varicella. *J. Pediatr. Ophthalmol. Strabismus* 27:221, 1990.
8. Jordan, D. R., Noel, L.-P., and Clarke, W. N.: Ocular involvement in varicella. *Clin. Pediatr.* 23:434, 1984.
9. Trantas, A.: Kératite superficielle exanthématique pendant la rougeole et d'autres maladies exanthématiques. *Bull. Soc. Fr. Ophtalmol.* 24:592, 1907.
10. Chow, Y.: Varizellen der Bindehaut. *Klin. Monatsbl. Augenheilkd.* 74:484, 1925.
11. Sallman, L.: Limbusknötchen bei varizellen. *Z. Augenheilkd.* 62:185, 1927.
12. Falls, H. F., and Beall, J. G.: Ocular varicella. Report of a case of corneal phlyctenule. *Arch. Ophthalmol.* 34:411, 1945.
13. Veeneklaas, G. M. H.: Recidiverende en corneo-sclerale varicellen. *Maandschr. Kindergeneesk.* 17:18, 1949.
14. Chan, E., and Mao, W. S.: Varicella involving the eye. *Chin. Med. J.* 68:375, 1950.
15. Capolongo, G.: Contributo all'interpretazione della cheratocongiuntivite flitennulare che si manifesta in alcune malattie infettive. *Boll. Ocul.* 29:443, 1950.
16. Postic, S.: Kératite varicelleuse. *Bull. Soc. Ophtalmol.* 70:127, 1957.

17. Cairns, J. E.: Varicella of the cornea treated with 5-iodo-2'-deoxyuridine. *Br. J. Ophthalmol.* 48:288, 1964.
18. Jervey, E. D., Armstrong, G. F., and Harkins, G.: Ocular varicella with particular reference to keratoconjunctival lesions. *South. Med. J.* 60:696, 1967.
19. Terson, A.: Notes thérapeutiques et cliniques. *Clin. Ophthalmol.* 10:190, 1904.
20. Oppenheimer, E. H.: Varicelle der Hornhaut. *Dtsch. Med. Wochenschr.* 31:833, 1905.
21. Wyler, J. S.: Corneal ulcer produced by varicella. *JAMA* 68:1476, 1917.
22. Rosenbaum, H. D.: Varicella and the cornea. A case report. *Am. J. Ophthalmol.* 26:53, 1943.
23. Billo, O. E.: Varicella of the cornea. With report of a case. *U.S. Navy Med. Bull.* 46:1901, 1946.
24. deAlmeida Rebouças, J.: Ceratite ulcerosa varicelica. *Rev. Bras. Oftalmol.* 5:105, 1946.
25. Gonçalves, D.: Ulcera de córnea na varicela. *Rev. Bras. Oftalmol.* 6:33, 1947.
26. Pillat, A.: Über die Mitbeteiligung der Hornhaut bei Varizellen. *Oest. Ophthalmol. Ges.* 5:32, 1960.
27. Hugonnier, R., Magnard, P., and Paufigue, L.: Kératite varicellique avec amblyopie traitée par kératoplastie lamellaire et rééducation visuelle. *Bull. Soc. Ophthalmol. Fr.* 69:795, 1956.
28. Ellenberger, C.: A case of phthisis bulbi due to chickenpox. *Arch. Ophthalmol.* 47:352, 1952.
29. Grüter, W.: Die Ätiologie der Keratitis disciformis. *Ber. Zussamm. Dtsch. Ophthalmol. Ges.* 48:209, 1930.
30. Pickard, R.: Varicella of the cornea. *Br. J. Ophthalmol.* 20:15, 1936.
31. Gözcü, N. I.: Three cases of disciform keratitis. *Turk. Oftalh. Gas.* 2:477, 1938.
32. Loewenstein, A.: Specific inflammation of the cornea in chickenpox. *Br. J. Ophthalmol.* 24:391, 1940.
33. Paufigue, L., Chauviré, E., and Barut, C.: La kératite varicellique. *J. Ophthalmol.* 3:133, 1944.
34. Paufigue, L., and Bonamour, G. A.: Un nouveau cas de kératite varicellique. *J. Ophthalmol.* 3:255, 1944.
35. Paufigue, L., and Bonamour, G.: La kératite varicellique. *J. Med. Lyon* 27:499, 1946.
36. Neame, H.: Virus diseases of the eye. *Trans. Ophthalmol. Soc. U.K.* 64:85, 1944.
37. Cavara, V.: Le manifestazioni oculari dell'infezione erpetica. *Boll. Ocul.* 25:1, 1946.
38. Frandsen, E.: Chickenpox in the cornea. *Acta Ophthalmol.* 28:113, 1950.
39. Cavara, V.: The role of viruses in the etiology of uveitis. *Acta XVII Concil. Ophthalmol.* 2:1232, 1955.
40. Moulié, H. B., and Gofanovich Baron, H.: Herpes corneano posterior (herpes de Schnyder). *Arch. Oftalmol. Buenos Aires* 25:43, 1950.
41. Thygeson, P., Hogan, M. J., and Kimura, S. J.: Observations on uveitis associated with viral disease. *Trans. Am. Ophthalmol. Soc.* 55:333, 1957.
42. Nesburn, A. B., Borit, A., Pentelei-Molnar, J., and Lazaro, R.: Varicella dendritic keratitis. *Invest. Ophthalmol.* 13:764, 1974.
43. Tessler, H. H., and Krimmer, B. M.: Disciform keratitis induced by varicella virus. *Eye Ear Nose Throat Mon.* 54:311, 1975.
44. Uchida, Y., Kaneko, M., and Hayashi, K.: Varicella dendritic keratitis. *Am. J. Ophthalmol.* 89:259, 1980.
45. Meyer, R. F., and Wolter, J. R.: Granulomatous inflammatory reaction to degenerating Descemet's membrane. *Ann. Ophthalmol.* 13:1113, 1981.
46. Wilson, F. M., II: Varicella and herpes zoster ophthalmicus. In Tabbara, K. F., and Hyndiuk, R. A. (eds.): *Infections of the Eye*. Boston, Little, Brown and Company, 1986, pp. 369-386.
47. Uchida, Y.: Varicella dendritic keratitis. In Darrell, R. W. (ed.): *Viral Diseases of the Eye*. Philadelphia, Lea & Febiger, 1985, pp. 73-77.
48. deFreitas, D., Kelly, L. D., Pavan-Langston, D., Sato, E. H., and Kenyon, K. R.: Delayed onset varicella keratitis. *Ophthalmology* 97:137, 1990.
49. Collier, M.: Formes cliniques tardives de la kératite varicellique. *Bull. Soc. Ophthalmol. Fr.* 65:397, 1952.
50. Tessler, H. H., and Krimmer, B. M.: Corticosteroids and varicella disciform keratitis. *Am. J. Ophthalmol.* 90:115, 1980.

Visual Field Defects in Diabetic Patients With Primary Open-Angle Glaucoma

John H. Zeiter, M.D., Dong H. Shin, M.D., and Nam H. Baek, M.D.

We reviewed the automated visual field tests of 110 nondiabetic and 87 diabetic patients with primary open-angle glaucoma randomly selected from a large glaucoma practice to investigate a possible qualitative difference in the pattern of visual field defects between nondiabetic and diabetic patients with primary open-angle glaucoma. A single reviewer analyzed, in masked fashion, the visual field tests of each patient and decided whether or not visual field defects were present mainly in the inferior half of the visual field. Of the 110 nondiabetic patients, 40 (36.4%) had visual field defects located mainly in the inferior half of the visual field in one or both eyes, whereas 56 of the 87 (64.4%) diabetic patients had such defects. This difference was statistically significant ($P = .0001$). We believe that a vascular factor, such as that attributable to diabetes mellitus, may influence glaucomatous optic nerve damage, thus causing a difference in the pattern of visual field loss in patients with primary open-angle glaucoma.

THE MOST FREQUENT early specific visual field defects in glaucoma are circumscribed paracentral scotomas in the central visual field, usually within the Bjerrum area, which may eventually progress to arcuate scotomas characteristic of nerve fiber bundle damage seen in patients with glaucoma.¹ Glaucomatous visual field defects are more common in the superior half than in the inferior half of the visual field in patients with early to moderate primary open-angle glaucoma.²⁻⁵ In many patients with primary open-angle glaucoma and diabetes mellitus, the inferior half of the visual field appears to be

more affected than the superior half. We investigated possible qualitative differences in the visual field defects between diabetic and nondiabetic patients with primary open-angle glaucoma.

Patients and Methods

We reviewed the charts of 485 nondiabetic and 495 diabetic patients randomly selected from a large glaucoma practice. Patients were included in the study if they had the following: primary open-angle glaucoma; no evidence of retinal abnormalities, including diabetic retinopathy, macular degeneration, and retinal vascular occlusion; and a reliable automated visual field test in at least one eye demonstrating Aulhorn's Stage 1, 2, or 3 visual field loss.⁶ In Stage 1, relative defects are seen in the arcuate area. Stage 2 shows spotlike deep defects still not connected with the blind spot; Stage 3 shows an arcuate scotoma, often with breakthrough into the nasal periphery, which produces a classic nasal step. We defined a reliable visual field test as one with fewer than 30% fixation losses and fewer than 33% false-positive and false-negative errors on automated visual field testing.⁷⁻⁹ These inclusion criteria avoided the possibility of selection bias during this initial screening. A total of 110 nondiabetic and 87 diabetic patients with primary open-angle glaucoma met the inclusion criteria for the study.

A single reviewer analyzed, in masked fashion, the visual field tests for each eye and decided whether visual field loss was more severe in the inferior half of the visual field. Visual field defects were considered more severe in the inferior half if the pattern deviation plot showed at least three more contiguous totally black probability symbols ($P = .005$) in the inferior half of the visual field. If a patient had more than one visual field test per eye, then the reviewer analyzed the earliest reliable visu-

Accepted for publication Feb. 12, 1991.

From the Kresge Eye Institute, Wayne State University, Detroit, Michigan.

Reprint requests to Dong H. Shin, M.D., Kresge Eye Institute, Wayne State University, 4717 St. Antoine, Detroit, MI 48201.

al field test that showed significant glaucomatous defects. If the first automated visual field test was not consistent with subsequent visual field tests, then the reviewer analyzed the second or third visual field test. If the visual field loss with a small stimulus size was complete or near complete and showed a preponderance of inferior or superior visual field loss with a larger stimulus size, then the reviewer analyzed the latter.

After analyzing the automated visual field tests, the reviewer recorded the patient's age, gender, and whether or not the patient had diabetes. If a patient had diabetes, the reviewer recorded the type (noninsulin-dependent diabetes mellitus or insulin-dependent diabetes mellitus).

Chi-square analysis was used for all statistical calculations.

Results

In the nondiabetic group, there were 56 men and 54 women with a mean age of 67.2 ± 10.9 years (range, 35 to 87 years). In the diabetic group, there were 32 men and 55 women with a mean age of 68.3 ± 8.9 years (range, 45 to 85 years). Sixty-five patients had noninsulin-dependent diabetes and 22 patients had insulin-dependent diabetes.

Of 110 nondiabetic patients with primary open-angle glaucoma, 40 (36.4%) showed defects located mainly in the inferior visual field in at least one eye, whereas 56 of 87 (64.4%) diabetic patients with primary open-angle glaucoma showed such visual field defects. This difference was statistically significant ($P = .0001$). Both men and women with primary open-angle glaucoma and diabetes had mainly inferior visual field defects significantly more often than the nondiabetic men and women with primary open-angle glaucoma ($P = .0292$ and $P = .0004$, respectively).

Of the 22 patients with insulin-dependent diabetes and the 65 patients with noninsulin-dependent diabetes, both groups had mainly inferior visual field defects significantly more often than nondiabetic patients with primary open-angle glaucoma ($P = .0004$ and $P = .0024$, respectively). Although a higher percentage of the patients with insulin-dependent diabetes than the patients with noninsulin-dependent diabetes had mainly inferior visual field defects

(17 of 22, 77.3% compared with 39 of 65, 60.0%), this difference was not statistically significant.

Discussion

The pattern of visual field loss in patients with primary open-angle glaucoma with and without diabetes showed a significant qualitative difference. Diabetic patients with primary open-angle glaucoma develop visual field defects mainly in the inferior half of the visual field more often than nondiabetic patients with primary open-angle glaucoma. Patients with primary open-angle glaucoma more commonly develop glaucomatous visual field defects in the superior half of the visual field.²⁻⁵ The preponderance of superior visual field defects in patients with primary open-angle glaucoma may be caused by less connective tissue support and larger pores in the inferoperipheral region of the lamina cribrosa.¹⁰

It is difficult to establish a specific mechanism by which diabetic patients with primary open-angle glaucoma develop defects mainly in the inferior visual field more often than nondiabetic patients with primary open-angle glaucoma. Several authors have suggested that vascular factors in addition to intraocular pressure may play an important role in the pathogenesis of glaucoma.¹¹⁻¹³ Unfortunately, it has been difficult to prove how and to what extent these factors influence nerve fiber damage and visual field abnormalities typically seen in patients with glaucoma. We can only speculate that a vascular factor may play a role in the difference in the pattern of visual field loss between patients with primary open-angle glaucoma with and without diabetes. Recently, investigators have found abnormally low capillary blood flow at the level of the optic nerve head in diabetic patients as compared to control subjects.¹⁴ It is possible, then, that pathologic alterations in the microvasculature of the optic disk in diabetic patients with primary open-angle glaucoma may influence the pattern as well as the development of visual field loss in these patients.

If a vascular factor such as that attributable to diabetes is responsible for an increase in the frequency of inferior visual field defects in patients with primary open-angle glaucoma and diabetes, then it is possible that this same

factor places these patients at an increased risk for visual field loss at a lower intraocular pressure than nondiabetic patients with primary open-angle glaucoma.¹⁵ Also, patients with primary open-angle glaucoma and other systemic vascular disease or patients who develop visual field defects from other known or suspected vascular disorders may show an increased frequency of inferior dominant visual field defects. The most frequent visual field defects in patients with nonarteritic anterior ischemic optic neuropathy are inferior altitudinal defects.¹⁶ Additionally, diabetic patients with disk swelling more frequently demonstrate inferior visual field defects.¹⁷⁻²¹

Although defects located mainly in the inferior half of the visual field occurred in 56 of 87 (64.4%) patients with primary open-angle glaucoma and diabetes, the remaining patients were not so affected. Therefore, there appears to be a spectrum of visual field defects involving varying amounts of the inferior and superior halves of the visual field. This considerable variation in the amount of inferior compared with superior visual field damage may be caused by variations in glucose control, duration of diabetes, extent of peripheral vascular disease, or any number of other factors that are difficult to control in a retrospective study.

Although we did not control for age in our randomly selected groups of patients with primary open-angle glaucoma, the mean ages of patients with and without diabetes were similar. The numbers of nondiabetic men and women with primary open-angle glaucoma were also similar, but there were nearly twice as many women as men with primary open-angle glaucoma and diabetes. This preponderance of women with primary open-angle glaucoma and diabetes has been reported by Christiansson.²² We found no significant difference between the numbers of men and women with primary open-angle glaucoma with or without diabetes who developed inferior dominant visual field defects.

The increased frequency of defects mainly in the inferior visual field was significant for both patients with primary open-angle glaucoma and insulin-dependent diabetes and patients with primary open-angle glaucoma and noninsulin-dependent diabetes. If a vascular factor such as that attributable to diabetes is responsible for the difference in location of visual field defects among patients with primary open-angle glaucoma, one might expect the patients

with insulin-dependent diabetes to show inferior visual field defects more often than those with noninsulin-dependent diabetes, since patients with insulin-dependent diabetes have a higher risk of systemic vascular disease than patients with noninsulin-dependent diabetes.²³ Our data show that a higher percentage of patients with primary open-angle glaucoma and insulin-dependent diabetes had inferior visual field defects than patients with primary open-angle glaucoma and noninsulin-dependent diabetes, but this difference was not statistically significant. This may be because of the small sample size of patients with primary open-angle glaucoma and insulin-dependent diabetes.

When examining patients with both diabetes and primary open-angle glaucoma, it is important to differentiate between visual field defects caused by the retinal microvascular changes of diabetes²⁴⁻²⁶ and those caused by the optic nerve damage of primary open-angle glaucoma. Although we excluded all patients with ophthalmoscopic evidence of retinopathy, Roth²⁷ reported that 32 of 66 (49%) diabetic patients without glaucoma and without clinical evidence of retinopathy showed relative isolated scotomas, presumably caused by localized areas of capillary closure visible only by fluorescein angiography. Such visual field defects in diabetic patients with minimal or no retinopathy tend to be localized in the superior quadrants of the visual field.²⁸ Therefore, the inferior visual field defects seen in the patients with primary open-angle glaucoma and diabetes in our study are more likely secondary to glaucomatous optic nerve damage rather than subclinical diabetic retinopathy.

References

1. Aulhorn, E., and Harms, H.: Early visual field defects in glaucoma. In Leydhecker, W. (ed.): *Glaucoma Symposium*. Tutzing Castle. Basel, S. Karger, 1967, pp. 151-186.
2. Furuno, F., and Matsuo, H.: Early stage progression in glaucomatous visual field changes. *Doc. Ophthalmol. Proc. Ser.* 19:247, 1979.
3. Hart, W. M., and Becker, B.: The onset and evolution of glaucomatous visual field defects. *Ophthalmology* 89:268, 1982.
4. Heijl, A., and Lundquist, L.: The frequency distribution of earliest glaucomatous visual field defects documented by automatic perimetry. *Acta Ophthalmol.* 62:658, 1983.

5. Harrington, D. O., and Drake, M. V.: Glaucoma. In: *The Visual Fields. Text and Atlas of Clinical Perimetry*, ed. 6. St. Louis, C. V. Mosby, 1990, pp. 179-218.
6. Aulhorn, E.: Visual field defects in chronic glaucoma. In Heilman, K., and Richardson, K. T. (eds.): *Glaucoma. Conceptions of a Disease. Pathogenesis, Diagnosis, Therapy*. Philadelphia, W. B. Saunders, 1968, pp. 157-168.
7. Katz, J., and Sommer, A.: Reliability indexes of automated perimetric tests. *Arch. Ophthalmol.* 106:1252, 1988.
8. Nelson-Quigg, J. M., Twelker, J. D., and Johnson, C. A.: Response properties of normal observers and patients during automated perimetry. *Arch. Ophthalmol.* 107:1612, 1989.
9. Johnson, C. A., and Nelson-Quigg, J. M.: Reliability of automated perimetric tests. *Arch. Ophthalmol.* 108:777, 1990.
10. Dandona, L., Quigley, H. A., Brown, A. E., and Enger, C.: Quantitative regional structure of the normal human lamina cribrosa. *Arch. Ophthalmol.* 108:393, 1990.
11. Minckler, D. S., and Spaeth, G. L.: Optic nerve damage in glaucoma. *Surv. Ophthalmol.* 26:128, 1981.
12. Hayreh, S. S.: Inter-individual variation in blood supply of the optic nerve head. *Doc. Ophthalmol.* 59:217, 1985.
13. Anderson, D. R.: Glaucoma. The damage caused by pressure. *Am. J. Ophthalmol.* 108:485, 1989.
14. Ogasawara, H. O., Feke, G. T., Yoshida, A., Goger, D. G., Busney, S. M., and McMeel, J. W.: Altered optic nerve head circulation in type I diabetes. ARVO abstracts. Supplement to *Invest. Ophthalmol. Vis. Sci.* Philadelphia, J. B. Lippincott, 1990, p. 137.
15. Becker, B.: Diabetes mellitus and primary open-angle glaucoma. *Am. J. Ophthalmol.* 71:1, 1971.
16. Repka, M. X., Savino, P. J., Schatz, N. J., and Sergott, R. C.: Clinical profile and long-term implications of anterior ischemic optic neuropathy. *Am. J. Ophthalmol.* 96:478, 1983.
17. Freund, M., Carmon, A., and Cohen, A. M.: Papilledema and papillitis in diabetes. *Am. J. Ophthalmol.* 60:18, 1965.
18. Appen, R. E., Chandra, S. R., Klein, R., and Myers, F. L.: Diabetic papillopathy. *Am. J. Ophthalmol.* 90:203, 1980.
19. Barr, C. C., Glaser, J. S., and Blankenship, G.: Acute disk swelling in juvenile diabetes. *Arch. Ophthalmol.* 98:2185, 1980.
20. Slavin, M. L.: Chronic asymptomatic ischemic optic neuropathy. A report of two cases in adults with diabetes mellitus. *J. Clin. Neuro. Ophthalmol.* 7:198, 1987.
21. Katz, B.: Disk swelling in an adult diabetic patient. *Surv. Ophthalmol.* 35:158, 1990.
22. Christiansson, J.: Glaucoma simplex in diabetes mellitus. *Acta Ophthalmol.* 43:224, 1965.
23. West, K. M.: *Epidemiology of Diabetes and Its Vascular Lesions*. New York, Elsevier, 1978, p. 372.
24. Taylor, E., and Dobree, J. H.: Proliferative diabetic retinopathy. Site and size of initial lesions. *Br. J. Ophthalmol.* 54:11, 1970.
25. Wisznia, K. I., Lieberman, T. W., and Leopold, I. H.: Visual fields in diabetic retinopathy. *Br. J. Ophthalmol.* 55:183, 1971.
26. Greite, J. H., Zumbansen, H. P., and Adamczyk, R.: Visual field in diabetic retinopathy (DR). In Greve, E. L., and Verriest, G. (eds.): *Fourth International Visual Field Symposium*. Hague, W. Junk, 1981, pp. 25-32.
27. Roth, J. A.: Central visual field in diabetes. *Br. J. Ophthalmol.* 53:16, 1969.
28. Trick, G. L., Trick, L. R., and Kilo, C.: Visual field defects in patients with insulin-dependent and noninsulin-dependent diabetes. *Ophthalmology* 97:475, 1989.

Blood-Cell Velocity in the Nailfold Capillaries of Patients With Normal-Tension and High-Tension Glaucoma

Paul Gasser, M.D., and Josef Flammer, M.D.

We compared the capillary blood-cell velocity in the fingertips of 30 patients with high-tension glaucoma, 30 patients with normal-tension glaucoma, and 30 control subjects by nailfold capillaroscopy. There were no measurable differences in the morphologic findings. The blood-flow velocity, however, was reduced significantly in the patients with normal-tension glaucoma compared with the control subjects ($P < .05$). This difference was especially pronounced after cold provocation ($P < .0005$). After cooling, 25 of 30 patients with normal-tension glaucoma had a blood standstill of 12 seconds or more, whereas only three of 30 control subjects and four of 30 patients with high-tension glaucoma had a measurable blood standstill.

GLAUCOMA is phenomenologically characterized by progressive excavation of the optic nerve head and visual field defects. The mechanisms that lead to the damage of the optic nerve head are not well understood. Clinical studies indicate that besides increased intraocular pressure, other factors might be involved. In addition to age, demographic, and genetic factors, mainly vascular and rheologic factors have been described.¹⁻⁷ An association between glaucoma and migraine⁸ as well as between glaucoma and peripheral circulation⁹⁻¹¹ has been reported. We compared the nailfold capillary blood flow under baseline conditions as well as after local warming and cooling in patients

with normal-tension glaucoma, patients with high-tension glaucoma, and control subjects.

Patients and Methods

We studied 30 patients with normal-tension glaucoma, 30 patients with high-tension glaucoma, and 30 control subjects (Table 1). Normal-tension glaucoma was defined as typical optic nerve head excavation and visual field defects with an untreated mean intraocular pressure of less than 21 mm Hg and a peak intraocular pressure of less than 25 mm Hg based on several diurnal pressure curves. High-tension glaucoma was defined as optic nerve head excavation and visual field defects with an untreated mean intraocular pressure greater than 24 mm Hg at repeated measurements.

We included patients with normal-tension glaucoma referred by other ophthalmologists to the University Eye Clinic during 1989 for clinical

TABLE 1
DEMOGRAPHIC DATA AND CLINICAL BACKGROUND OF CONTROL SUBJECTS AND PATIENTS*

	CONTROL SUBJECTS (N = 30)	PATIENTS WITH HIGH-TENSION GLAUCOMA (N = 30)	PATIENTS WITH NORMAL-TENSION GLAUCOMA (N = 30)
Sex (female: male)	18:12	17:13	16:14
Age (years)	59.2 ± 12.7	58.6 ± 11.9	60.6 ± 11.7
Pulse rate, sitting (per minute)	74.0 ± 14.5	73.0 ± 12.6	74.2 ± 10.1
Systolic blood pressure, sitting (mm Hg)	132.8 ± 20.4	127.1 ± 15.5	131.6 ± 23.9
Diastolic blood pressure, sitting (mm Hg)	82.8 ± 9.2	82.3 ± 9.7	82.5 ± 13.1

*Values given are mean ± standard deviation.

Accepted for publication Feb. 11, 1991.

From the Department of Internal Medicine, St. Clara-hospital, Basel, Switzerland (Dr. Gasser); and Department of Ophthalmology, University of Basel, Basel, Switzerland (Dr. Flammer). This study was supported by the Swiss National Science Foundation, grant No. 32-9367-87.

Reprint requests to Josef Flammer, M.D., Department of Ophthalmology, University of Basel, Mittlere Strasse 91, CH-4056 Basel, Switzerland.

cal examination. The conditions were either newly diagnosed (20 of 30 patients) or the patients had progressive visual field loss (ten of 30). Five patients were taking beta-blockers, even though their intraocular pressure had never been increased.

For each patient with normal-tension glaucoma included, a patient with high-tension glaucoma and a control subject of the same age were selected. The patients with high-tension glaucoma were also referred to us by other ophthalmologists for examination because of increased intraocular pressure despite treatment, progressing visual field loss, or both. All patients were taking antiglaucoma medication, including beta-blockers (25 of 30), miotics (17 of 30), or epinephrine derivatives (five of 30). The systemic carbonic anhydrase-inhibitor therapy (four of 30) was discontinued for at least 14 days before the test.

The control group consisted of 11 staff members of the hospital and 19 patients referred to us for cataract surgery. They all had normal intraocular pressure and normal-appearing optic nerve heads.

Exclusion criteria for all groups were migraine, anemia, cardiovascular diseases, systemic hypertension and hypotension, diabetes mellitus, and collagen or vascular disorders. The three groups were matched by age. Blood pressure and pulse rate were influenced by the exclusion criteria. The three groups, however, resembled each other in this respect merely by chance. None of the subjects had been taking any systemic medication for at least two weeks before the examination.

The nailfold capillaries were studied with the help of an incident-light microscope attached

to a television monitor.¹¹⁻¹³ To measure the diameter of the capillaries, photographs were taken from the monitor. To measure the capillary blood-cell velocity, the television pictures were videotaped and analyzed during playback by the flying-spot technique as previously described.^{14,15}

The examinations were performed in a room with a constant temperature of 23 C. Before participating in the investigation, the subjects were acclimatized in this room for 30 minutes. Thereafter, the videotape pictures were made to measure the morphologic variables. Then, the baseline blood-cell velocity was measured. After immersion of the fingertip in a warm-water bath of 40 C for three minutes, the second reading was performed. The third measurement was made after cooling the observed skin area for 60 seconds by blowing decompressed carbon dioxide of approximately -15 C over the nailfold. The fourth and the fifth measurements were made after spontaneous recovery periods of one and two minutes, respectively.¹² In cases where the blood flow ceased during local cooling, the duration of the blood-flow standstill was measured in seconds. Such cases are called vasospastic.¹¹

Results

To illustrate examples of the effect of cooling, photographs were taken from the videomonitor (Fig. 1). The morphologic characteristics of the individual capillaries were similar in the three groups. The arterial, venous, and crest diameters as well as the width of the loop were not



Fig. 1 (Gasser and Flammer). Photographs taken from the videomonitor demonstrating the nailfold capillaries after cold provocation. Left, A control subject with normal circulating erythrocytes. Right, Blood standstill and segmentation of the blood-cell column caused by flow stop after cooling (cold-induced vasospasm) in a patient with normal-tension glaucoma.

TABLE 2
MORPHOLOGIC FINDINGS ON NAILFOLD
CAPILLARIES*

	CONTROL SUBJECTS	PATIENTS WITH HIGH-TENSION GLAUCOMA	PATIENTS WITH NORMAL-TENSION GLAUCOMA
Diameter (μm)			
Arteriolar	11.1 \pm 2.1	11.0 \pm 1.8	10.6 \pm 1.8
Venular	13.0 \pm 2.5	13.3 \pm 2.3	12.7 \pm 2.0
Crest	16.0 \pm 3.4	16.3 \pm 3.5	16.5 \pm 2.9
Width	34.3 \pm 5.8	33.9 \pm 6.3	32.8 \pm 5.1
Capillary density (number of nail- fold capillary loops per mm) [†]	6.8 \pm 1.2	6.0 \pm 1.5	7.1 \pm 1.8

*Values given are mean \pm standard deviation.

[†]Significance level between control subjects and patients with high-tension glaucoma, $P = .026$.

significantly different (Table 2). The capillary density was slightly smaller in the high-tension glaucoma group than in the control group, which was statistically significant ($P = .026$). The capillary density in the normal-tension glaucoma group, however, was not significantly different from that in the control group.

The control group showed the well-known increase in the mean capillary blood-cell velocity after warming and a decrease after cooling the fingertip and during the recovery (Fig. 2). The patients with high-tension glaucoma showed the same basic dynamics (Fig. 2). In most instances, the patients with high-tension

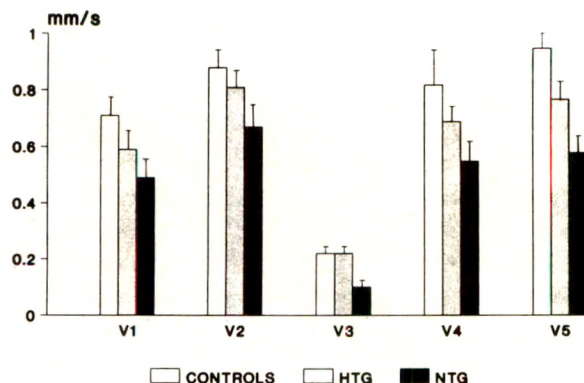


Fig. 2 (Gasser and Flammer). Blood-flow velocities of control subjects, patients with high-tension glaucoma (HTG), and patients with normal-tension glaucoma (NTG) at baseline (V1), after the warm-water bath (V2), after cooling (V3), and after recovery (V4 and V5).

glaucoma had on the average a slightly slower capillary blood-cell velocity, although these differences were not statistically significant.

The reduction of the capillary blood-cell velocity, however, was more pronounced in the normal-tension glaucoma group. The differences from the control subjects were statistically significant in all instances ($P < .05$), especially after cold provocation ($P < .0005$). Three control subjects and four patients with high-tension glaucoma had a measurable blood-flow standstill (Fig. 3). Of the 30 patients with normal-tension glaucoma, however, only five patients had no blood-flow stop and 25 patients had a clear blood-flow standstill, the duration of which ranged between ten and 95 seconds.

Discussion

The peripheral blood flow in patients with high-tension and normal-tension glaucoma might be different from that in normal subjects. The capillary blood-cell velocity was on the

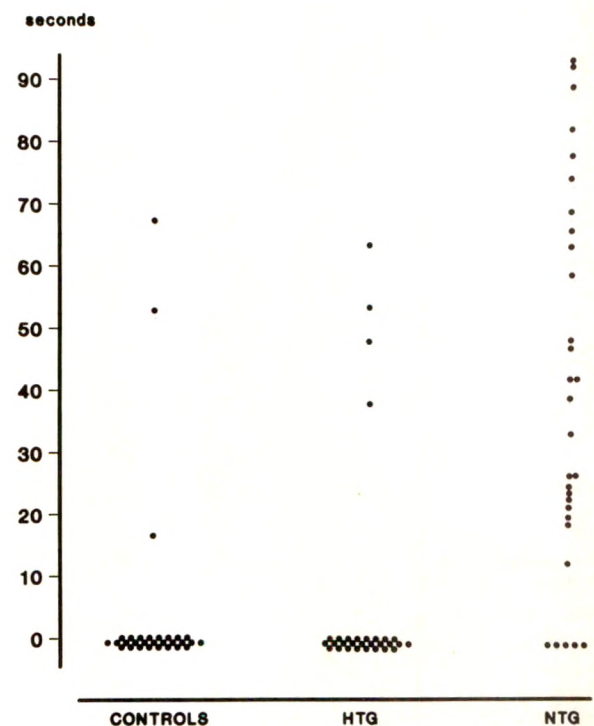


Fig. 3 (Gasser and Flammer). Duration (in seconds) of cold-induced blood-flow standstill in the control subjects, patients with high-tension glaucoma (HTG), and patients with normal-tension glaucoma (NTG).

average slightly slower in the patients with high-tension glaucoma than in normal control subjects, although this difference was not statistically significant. The normal-tension glaucoma group, however, had a more pronounced and statistically significant decrease in the capillary blood-cell velocity. The difference from the control subjects was especially evident after the cold provocation. The most striking finding, however, was the difference in blood-flow standstill after cooling. In this respect, patients with high-tension glaucoma and control subjects were essentially the same. The patients with normal-tension glaucoma, however, had a clear and statistically significant difference in blood-flow standstill.

It is difficult to know how much the population tested is representative of the total population. All the patients selected from our clinic were referred by other ophthalmologists. Some of these ophthalmologists knew that we had a special interest in vasospastic disorders. Therefore, we cannot exclude the possibility that the proportion of vasospastic cases in the population tested was slightly higher than that in an average population.

Nevertheless, these findings indicate that a pathologic vascular reaction called a vasospastic disorder¹⁴ most probably occurs more often in patients with normal-tension glaucoma than in control subjects or patients with high-tension glaucoma. This supports the hypothesis that vasospasm may be involved in the pathogenesis of normal-tension glaucoma.^{16,17} These findings are in agreement with the observations of Drance and associates⁹ and may have major therapeutic implications. It is possible that treatment of this vasospastic disorder may be beneficial to patients with normal-tension glaucoma, as has been previously reported.¹⁸⁻²¹

References

1. Demailly, P., Cambien, P., Plouin, P. F., Baron, P., and Chevallier, B.: Do patients with low-tension glaucoma have particular cardiovascular characteristics? *Ophthalmologica* 188:65, 1984.
2. Carter, C. J., Brooks, D. E., Doyle, D. L., and Drance, S. M.: Investigations into a vascular etiology for low-tension glaucoma. *Ophthalmology* 97:49, 1990.
3. Drance, S. M., Sweeny, V. P., Morgan, R. W., and Feldman, F.: Studies of factors involved in the production of low-tension glaucoma. *Arch. Ophthalmol.* 89:457, 1973.
4. Freyler, H., and Menapace, R.: Ist die Erblindung an Glaukom vermeidbar? *Spektrum Augenheilkd.* 2:121, 1988.
5. Goldberg, I., Hollows, F. C., Kass, M. A., and Becker, B.: Systemic factors in patients with low-tension glaucoma. *Br. J. Ophthalmol.* 65:56, 1981.
6. Trope, G. E., Salinas, S. A., and Glynn, M.: Blood viscosity in primary open-angle glaucoma. *Can. J. Ophthalmol. Vis. Sci.* 22:202, 1987.
7. Worch, A., and Kästner, R.: Das Glaukom ohne Hochdruck. *Folia Ophthalmol.* 10:221, 1985.
8. Phelps, D., and Corbett, J. J.: Migraine and low-tension glaucoma. A case-control study. *Invest. Ophthalmol. Vis. Sci.* 26:1105, 1985.
9. Drance, S. M., Douglas, G. R., Wijsman, K., Schulzer, M., and Britton, R. J.: Response of blood flow to warm and cold in normal and low-tension glaucoma patients. *Am. J. Ophthalmol.* 105:35, 1988.
10. Gasser, P., Flammer, J., Guthauser, U., and Mahler, F.: Do vasospasms provoke ocular diseases? *Angiology* 41:213, 1990.
11. Guthauser, U., Flammer, J., and Mahler, F.: The relationship between digital and ocular vasospasm. *Graefes Arch. Clin. Exp. Ophthalmol.* 226:224, 1988.
12. Bollinger, A., and Fagrell, B.: *Clinical Capillaroscopy*. Toronto, Hogrefe-Huber, 1990, pp. 1-30.
13. Gasser, P.: Capillary blood cell velocity in finger nailfold. Characteristics and reproducibility of the local cold response. *Microvasc. Res.* 40:29, 1990.
14. Mahler, F., Saner, H., Würbel, H., and Flammer, J.: Local cooling test for clinical capillaroscopy in Raynaud's phenomenon, unstable angina, and vasospastic visual disorders. *Vasa* 18:201, 1989.
15. Boss, C., Schnewly, P., and Mahler, F.: Evaluation and clinical application of the flying-spot method in nailfold capillary TV-microscopy. *Int. J. Microcirc. Clin. Exp.* 6:15, 1987.
16. Flammer, J., Guthauser, U., and Mahler, M.: Do ocular vasospasms help cause low-tension glaucoma? *Doc. Ophthalmol. Proc. Ser.* 49:397, 1987.
17. Gasser, P., and Flammer, J.: Influence of vasospasm on visual function. *Doc. Ophthalmol.* 66:3, 1987.
18. Flammer, J., and Guthauser, U.: Behandlung chorioidaler Vasospasmen mit Kalziumantagonisten. *Klin. Monatsbl. Augenheilkd.* 190:299, 1987.
19. Gasser, P., and Flammer, J.: Short- and long term effect of nifedipine on the visual field in patient with presumed vasospasm. *J. Int. Med. Res.* 18:334, 1990.
20. —: Die dynamisch-video-kapillarmikroskopische Beeinflussung akraler und okulärer Vasospasmen durch Kalzium- und Serotoninantagonisten. *Vasa* 27:79, 1989.
21. Kitazawa, Y., Shirai, H., and Go, F. J.: The effect of Ca²⁺-antagonist on visual field in low-tension glaucoma. *Graefes Arch. Clin. Exp. Ophthalmol.* 227:408, 1989.

In Vitro Videographic Comparison of Argon and Nd:YAG Laser Iridotomy

Bruce E. Prum, Jr., M.D., Steven R. Shields, M.D., M. Bruce Shields, M.D.,
Dyson Hickingbotham, and David B. Chandler, B.S.

We used an *in vitro* technique with high-magnification video recording to evaluate from the posterior side of the iris the immediate sequence of events during argon and Nd:YAG laser peripheral iridotomy. The observed effects differed strikingly. The argon laser caused a gradual mounding up of iris pigment epithelium with each successive energy application before final penetration. This effect was reduced but not eliminated with higher power levels. The Nd:YAG laser caused complete disruption and dispersal of the pigment epithelium with a single pulse of energy. Additionally, a multiple focal point configuration of the Nd:YAG laser was observed to produce a significantly larger iridotomy than a single focal point configuration for comparable energy settings. These observations may in part explain the observed clinical advantage of the Nd:YAG laser over the argon laser for creation of a patent iridotomy.

LASER SURGICAL IRIDOTOMY has replaced incisional surgical iridectomy as the procedure of choice in the treatment of primary angle-closure glaucoma. During the 1970s, continuous-wave argon laser was most commonly used. In the 1980s, the Nd:YAG laser was introduced and was found to have a number of advantages over the argon laser. Among the advantages cited are the following: a much lower closure rate of initially patent iridotomies; the ability to penetrate the iris easily regardless of color; a shorter treatment time required with fewer laser applications and less

total energy delivery; reduced pupillary distortion and iritis; and increased patient comfort and tolerance for the procedure.¹⁻⁴

Comparative studies of argon and Nd:YAG laser iridotomies have been limited to visualization of the anterior iris surface in clinical situations and to time-limited histologic specimens with the potential for fixation artifacts. Clinical studies have disclosed a closure rate of argon laser iridotomies between 16% and 35%,¹⁻⁶ whereas Nd:YAG laser iridotomies usually close only in cases of iris neovascularization or uveitis.⁷ These observations have been postulated to result from the difference in energy delivery of the two lasers and the subsequent proliferation of remaining iris pigment epithelial cells left at the posterior side of the iridotomy opening.¹ To add further understanding to this question, we performed a videographic comparison of the real-time effects of argon and Nd:YAG laser iridotomy on the posterior iris in human autopsy eyes.

Material and Methods

Our video recording system is similar to previously described techniques of Miyake and Miyake⁸ and Apple and associates⁹ for posterior photography in human autopsy eyes. A long-distance microscope was mounted on a portable slit lamp to give par focal illumination. A black-and-white, charged-coupled device, high-resolution video camera was mounted on a 32-mm objective at the viewing port of the microscope. A video recorder and monitor captured images of the laser effects. This apparatus was placed near the laser to allow real-time viewing of the posterior iris during laser iridotomy with a $\times 90$ magnification.

Human autopsy eyes were obtained from the local eye bank and used within 12 to 48 hours after enucleation. Only phakic eyes without

Accepted for publication Feb. 21, 1991.
From the Department of Ophthalmology, Duke University Eye Center, Durham, North Carolina.
Reprint requests to M. Bruce Shields, M.D., Duke University Eye Center, P.O. Box 3802, Durham, NC 27710.

previous iridotomies were used. The globe was trimmed of adherent conjunctiva, extraocular muscles, and fat and was fixed securely with cyanoacrylate glue in a Plexiglas plate with cornea, corneoscleral limbus, and a small amount of sclera protruding through the opening in the plate. With the cornea side down, the posterior segment was cut flush to the plate with Westcott scissors, leaving vitreous within the remaining anterior segment. The lens zonules were severed with a surgical blade, and the lens was removed with forceps without disturbing the iris. Saline was added to the remaining vitreous in the anterior segment to fill it up to the scleral rim, and a square glass slide was placed carefully over the cut portion of the eye to avoid trapping air under the slide. The slide was then cemented to the plate to create a watertight seal and to allow a clear view of the posterior iris. Next, the preparation was turned over with the cornea placed upward. The cornea was removed at the corneoscleral limbus with Westcott scissors to improve visualization of the anterior iris. A Plexiglas ring was then cemented to the plate around the open anterior segment; the resulting well was filled with saline; and another square glass slide was secured over the ring to create an artificial anterior chamber. The entire anterior segment preparation was then mounted at the argon or Nd:YAG laser in the usual anteroposterior orientation of a patient for delivery of laser energy to the anterior iris. Video recordings were made from the posterior side of the iris with the previously described system.

For creation of iridotomies, no contact lens was used. Laser energy was delivered directly through the glass slide to the anterior side of the iris in the preparation mounted at the laser. A continuous-wave argon laser was used for the argon laser iridotomies. To penetrate the iris stroma, settings of 500, 1,000, or 1,500 mW with a 50- μ m spot size and 0.1-second duration were chosen, and sufficient pulses were delivered to reach the iris pigment epithelium. To penetrate the pigment epithelium, 1,000-mW, 100- μ m spot size, and 0.1-second duration settings were used, and sufficient pulses were delivered to create a patent iridotomy as viewed anteriorly by the surgeon. A pulsed Nd:YAG laser was used for the Nd:YAG laser iridotomies. Settings included a 12-nsec duration, no offset between the aiming and therapeutic beams, and energy settings of 5.7, 9.8, and 14.5 mJ. Fundamental mode (single focal point configuration with approximately 7- μ m spot size)

and multimode (multiple focal point configuration with approximately 70- μ m spot size) settings were compared at each of the energy levels studied, along with one, two, and four pulses per burst. Both argon and Nd:YAG laser iridotomies were performed on the same eyes to control for variability between specimens.

To quantify more precisely the effects of the argon laser and fundamental mode and multimode settings on the Nd:YAG laser in disrupting the iris pigment epithelium, the area of the iris transillumination defects created by the laser pulses was measured on the posterior iris surface. Video images of iris transillumination defects were enhanced and the area of these defects was calculated using a JAVA (Jandel Scientific, Cortes Madera, California) computer video image analysis program.

Results

Dynamic in vitro recording of argon and Nd:YAG laser iridotomies disclosed striking differences in the effects of the two lasers on the iris pigment epithelium. The Nd:YAG laser caused an instantaneous and explosive disruption of the epithelial layer with a marked backward and forward movement of the entire iris at the moment of laser impact. Multiple small clumps of pigment epithelium were seen to shoot rapidly away from the treatment site and rain down in the vitreous and saline behind the iris (Fig. 1). The resulting iris defects, although often with jagged edges, showed complete absence of pigment epithelium at the iridotomy site. This effect was seen at all energy settings but was most pronounced with the multimode setting at 14.5 mJ for four pulses per burst. At lower energy settings of 5.7 and 9.8 mJ and one or two pulses per burst in the fundamental mode, the iris transillumination defects were smaller than those created with the same settings in multimode (Fig. 2). The measured areas of transillumination defects were compared with the various settings at one and two pulses per burst (Table). These differences were essentially negated at four pulses per burst for either fundamental mode or multimode at any energy setting, with the defects ranging from 2.2 to 3.2 mm² in size.

By contrast, argon laser iridotomies with stromal settings at 500 mW, 50- μ m spot, 0.1 second caused gradual contraction of the iris pigment epithelium into a small mound at the

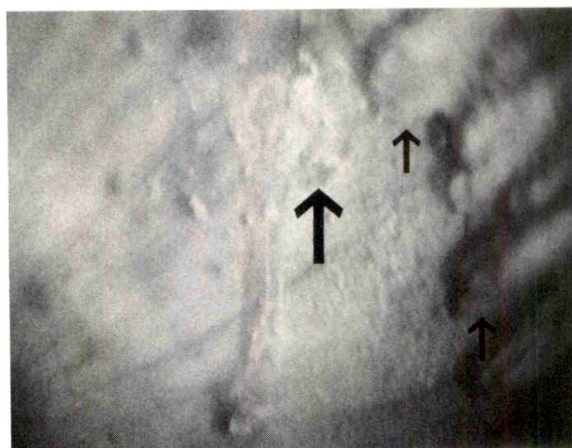
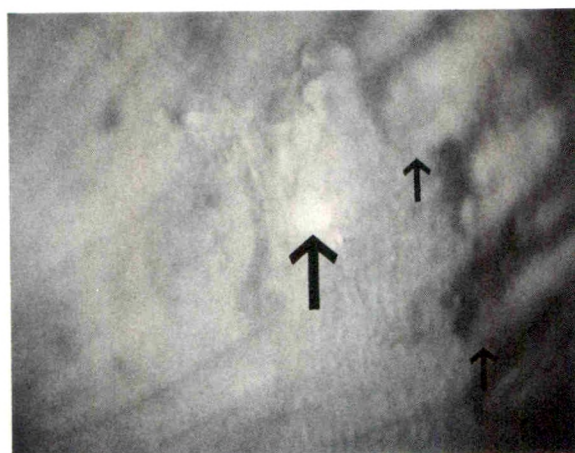


Fig. 1 (Prum and associates). *Left*, View of posterior iris immediately after Nd:YAG laser impact at 5.7 mJ, two pulses per burst in multimode with iridotomy transilluminated (large arrow). *Right*, an instant later (large arrow indicates iris pigment epithelial defect). Note the small clumps of pigment epithelium suspended in the saline behind the iris that progressively stream downward in the time elapsed. Small arrows indicate ciliary processes.

site of the eventual iridotomy opening. Pigment was not dispersed as the laser penetrated first the stroma and then the epithelial layer at settings of 1,000 mW, 100- μ m spot, 0.1 second. The pigment remained mounded up at the posterior edge of the iridotomy opening, which measured 0.7 mm² and appeared able to fall mechanically into the opening or migrate over it (Fig. 3). At the higher settings of 1,500 mW, 50- μ m spot, 0.1 second, penetration of the

stroma required fewer applications and was associated with much less mounding up of pigment epithelium around the posterior edge of the iridotomy opening. Pigment epithelial perforation was achieved with an average of five additional applications, and the resulting iridotomy was 1.5 mm², although the pigment remained in small clumps around the posterior edge of the iridotomy (Fig. 4).

Discussion

Miyake and Miyake⁸ described a technique for 16-mm cinematography of posterior chamber intraocular lens haptic fixation in human cadaver eyes. Apple and associates⁹ subsequently described an expanded technique for posterior visualization, which included videotape recording, 35-mm still photography, and

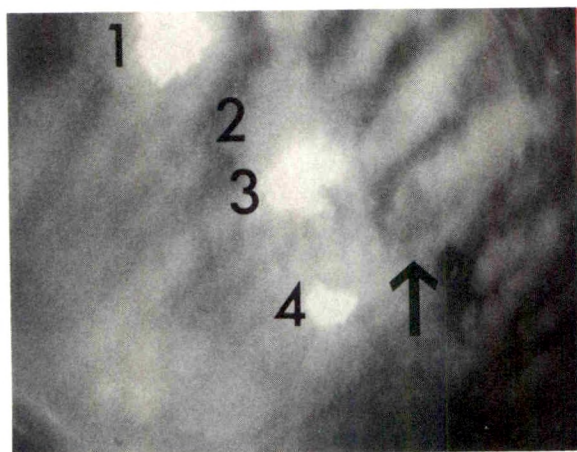


Fig. 2 (Prum and associates). View of posterior iris with transillumination showing four Nd:YAG iridotomies created at 5.7 mJ, one pulse per burst, in multimode (1) and fundamental mode (2) (defect obscured by cloud of pigment in this frame), and two pulses per burst, in multimode (3) and fundamental mode (4). The radially oriented ciliary processes (large arrow) and iris folds are also seen.

TABLE
AREA OF Nd:YAG TRANSILLUMINATION DEFECTS (mm²)

	FUNDAMENTAL MODE		MULTIMODE	
	1 PULSE PER BURST	2 PULSES PER BURST	1 PULSE PER BURST	2 PULSES PER BURST
5.7 mJ	0.04	0.29	0.87	1.52
9.8 mJ	0.07	0.34	1.01	1.49
14.5 mJ	0.61	0.90	0.60	1.61

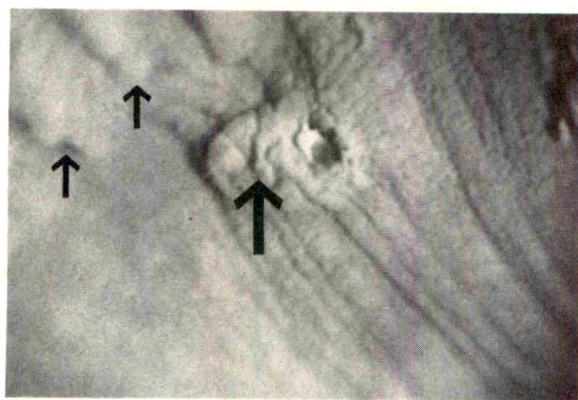


Fig. 3 (Prum and associates). Posterior view of argon laser iridotomy created with settings at 500 mW, 50- μ m spot, 0.1 second. Note the large mound of pigment epithelium (large arrow) around the iridotomy opening created at this energy setting. Radial iris folds and the edge of several ciliary processes (small arrows) are also seen.

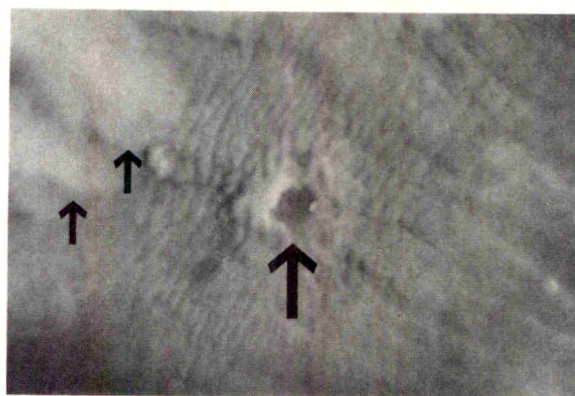


Fig. 4 (Prum and associates). Posterior view of argon laser iridotomy created at settings of 1,500 mW, 50- μ m spot, 0.1 second. Small clumps of pigment epithelium surround the iridotomy (large arrow). The ends of two ciliary processes are seen (small arrows).

high-magnification zoom stereomicroscopy. They used this technique to observe and teach cataract surgery, with focus on the zonules and posterior capsule during extracapsular cataract extraction or phacoemulsification, and to evaluate design, insertion, and positioning of new intraocular lenses and insertion devices.

Our apparatus for video acquisition is similar to that of Miyake and Miyake⁸ and has enabled us to obtain unique, high-magnification, dynamic views of the posterior iris during laser iridotomy. Using an anterior segment iris preparation from human autopsy eyes, we compared the real-time effects of argon and Nd:YAG lasers on the iris pigment epithelium during laser iridotomy. Our system lacks color video and still photography, but the black-and-white video resolution at high magnification is excellent for quantitative and qualitative evaluations of laser effects.

The system is also limited because it does not fully reproduce the clinical setting, since the cornea has been removed from the autopsy eyes, and no contact lens was used to focus the laser energy. Nevertheless, our technique has been useful in evaluating real-time effects of laser iridotomies as viewed from the posterior iris surface.

Clinical investigators have observed a much higher rate of iridotomy closure with the argon laser as compared to the Nd:YAG laser.¹⁻⁴ Although the occluded iridotomy can usually be reopened easily, it nevertheless subjects the patient to the risk of an acute angle-closure

attack and the need for further laser surgery. Theories regarding the increased closure rate of argon laser iridotomies have been based on clinical and histologic observations. Robin and Pollack¹ theorized that the thermal energy of the argon laser disrupts iris pigment epithelial cells and stimulates proliferation, whereas the shock wave of the Nd:YAG laser disrupts and jars loose the surrounding pigment epithelium, which leaves few bordering cells to proliferate and close off the iridotomy opening. Histologic evaluation in humans, monkeys, and rabbits has shown closure of iridotomies by bridging iris pigment epithelium.^{5,9,10}

Our study showed a marked difference in the way the epithelial layer reacts dynamically to the energy delivery of the two lasers. With low-energy argon laser settings, the iris pigment epithelial layer contracts slowly with each successive laser application into an elevated mound beneath the developing iridotomy. Finally, the argon beam penetrates the epithelial layer but does so directly through the large mound of pigmented tissue without much evident disruption. One can postulate that this tissue might dislodge mechanically at a later date to obstruct the iridotomy in the in vivo setting. Alternatively, because of its close proximity to the opening, the iris pigment epithelium might actually proliferate or migrate across the opening in association with a scarring/healing reaction. With higher-energy argon laser settings, the mounding up of pigment epithelium is not as pronounced. Theoretically

this occurs because the epithelial layer tissue has less time to contract centripetally around the iridotomy site before the laser beam penetrates the iris to form a patent iridotomy. Nevertheless, small clumps of pigment epithelium are seen around the posterior edges of the iridotomy even at the higher energy settings, which could also obstruct the iridotomy mechanically.

Based on our findings, one might expect lower-energy argon laser iridotomies to close more frequently than higher-energy laser iridotomies. Clinically, one can usually reduce the risk of closure of the argon laser iridotomy by creating a large opening, which is less likely to be obstructed by the pigment epithelium. The increased number of laser applications that this usually requires, however, increases the potential for damage to cornea, iris, lens, and retina, as well as the risk of intraocular pressure increase and iritis. It may be that higher energy settings with fewer total applications would reduce the chances of iridotomy closure without increasing the potential for the other complications, although further clinical study is needed to confirm this.

In contrast to the argon laser, the Nd:YAG laser caused marked disruption of the iris pigment epithelium with complete, focal ejection of the tissue from the site of laser application. The pigment epithelium was seen to shoot rapidly away from the posterior iris at the moment of laser impact, which left a variably jagged-edged but complete iris defect without the formation of a small mound or residual clumps of pigment epithelium around the iridotomy opening, as was seen with use of the argon laser.

Rodrigues and associates¹¹ noted that in human eyes there is minimal evidence of inflammation around Nd:YAG iridotomies, and they have postulated that this relative lack of inflammatory response, compared to the severe response seen around argon laser iridotomies, may explain the lower rate of subsequent reactive fibrosis and closure of the Nd:YAG iridotomies. Goldberg, Tso, and Mirolovich¹² confirmed these histologic findings in human eyes. Our findings, however, are more consistent with the theory of Robin and Pollack,¹ who postulated that argon laser energy may change iris pigment epithelial cells and stimulate cell proliferation, whereas Nd:YAG laser energy jars cells away from the iridotomy site. Although in our system we cannot see cellular changes that might stimulate cell proliferation,

we do see the striking differences in dynamic changes of the iris pigment epithelium at and surrounding the iridotomy site during argon and Nd:YAG treatments.

We also compared the sizes of iris transillumination defects created with a single laser application in the fundamental mode and multimode settings of the Q-switched Nd:YAG laser. At the lowest energy settings of 5.7 and 9.8 mJ with one and two pulses per burst, the multimode produced openings that were severalfold larger than those created by comparable settings with the fundamental mode. However, the differences were negligible with higher energy levels or with four pulses per burst. These dynamic in vitro comparisons suggest that an adequate iridotomy can be created with energy settings of approximately 6 to 8 mJ and two pulses per burst in the multimode setting.

The forceful and complete dislodging of the pigment epithelium caused by the explosive effect of the Nd:YAG laser contributes significantly to the long-term patency of these iridotomies. In contrast, the pigment epithelium at the argon laser iridotomy site is in a position to allow for closure by whatever that mechanism may be.

References

1. Robin, A. L., and Pollack, I. P.: A comparison of neodymium:YAG and argon laser iridotomy. *Ophthalmology* 91:1011, 1984.
2. McAllister, J. A., Schwartz, L. W., Moster, M., and Spaeth, T. L.: Laser peripheral iridectomy comparing Q-switched neodymium YAG with argon. *Trans. Ophthalmol. Soc. U.K.* 104:67, 1984.
3. Moster, M. R., Schwartz, L. W., Spaeth, T. L., Wilson, R. P., McAllister, J. A., and Poryzees, E. M.: Laser iridectomy. A controlled study comparing argon and neodymium:YAG. *Ophthalmology* 93:20, 1986.
4. Del Priore, L. V., Robin, A. L., and Pollack, I. P.: Neodymium:YAG and argon laser iridotomy. *Ophthalmology* 95:1207, 1988.
5. Pollack, I. P.: Use of argon laser energy to produce iridotomies. *Trans. Am. Ophthalmol. Soc.* 77:674, 1979.
6. Podos, S. M., Kels, V. D., Moos, A. P., Ritch, R., and Anders, M. D.: Continuous wave argon laser iridectomy in angle-closure glaucoma. *Trans. Am. Ophthalmol. Soc.* 77:51, 1979.
7. Klapper, R. M.: Q-switched neodymium:YAG laser iridotomy. *Ophthalmology* 91:1017, 1984.
8. Miyake, K., and Miyake, C.: Intraoperative pos-

terior chambers lens haptic fixation in the human cadaver eye. *Ophthalmic Surg.* 16:230, 1985.

9. Apple, D. J., Lim, E. S., Morgan, R. C., Tsai, J. C., Gwin, T. D., Brown, S. J., and Carlson, A. N.: Preparation and study of human eyes obtained post mortem with the Miyake posterior photographic technique. *Ophthalmology* 97:810, 1990.

10. Dragon, D. M., Robin, A. L., Pollack, I. P., Quigley, H. A., Green, W. R., Murray, T. G., Hotchkiss, M. L., and D'Anna, S.: Neodymium:YAG laser

iridotomy in the cynomolgus monkey. *Invest. Ophthalmol. Vis. Sci.* 26:789, 1985.

11. Rodrigues, M. M., Spaeth, T. L., Moster, M., and Hackett, J.: Histopathology of neodymium:YAG laser iridectomy in humans. *Ophthalmology* 92:1696, 1985.

12. Goldberg, M. F., Tso, M. O. M., and Mirolovich, M.: Histopathological characteristics of neodymium-YAG laser iridotomy in the human eye. *Br. J. Ophthalmol.* 71:623, 1987.

OPHTHALMIC MINIATURE

Still one more point about Lincoln that concerns his eyes. To my grandmother, who once wished to show him the flowers in her front yard, he said: "I will look at your flowers, mother, but I really cannot understand what people see to admire in such things. I am somehow deficient." From this I have often suspected that Lincoln was color-blind. He would often enough, in conversation and in public speeches, refer to the sunset, the flowers, and so on, but only, as it seemed, because these matters appeared beautiful to others.

Thomas Hall Stastid, *My Father Knew Lincoln*
The Nation 128:228, 1929

Scleral Buckling for Rhegmatogenous Retinal Detachment Associated With Severe Myopia

Francisco J. Rodriguez, M.D., Hilel Lewis, M.D., Allan E. Kreiger, M.D.,
Marc O. Yoshizumi, M.D., and Yossi Sidikaro, M.D.

From Jan. 1, 1980, to Dec. 31, 1989, we performed scleral buckling surgery on 48 eyes of 46 patients for rhegmatogenous retinal detachments associated with severe myopia (greater than 5.00 diopters). Forty eyes of 38 patients were observed for at least six months, and the mean follow-up period was 46 months. Intraoperative complications occurred in four of 48 eyes (8%) and included retinal incarceration (two eyes), choroidal hemorrhage (one eye), and choroidal detachment (one eye). Three of the 40 eyes (7.5%) followed up for more than six months developed a recurrent retinal detachment and underwent a revision of the scleral buckle. At the last follow-up examination, the retinas of all 40 eyes were totally reattached. Final visual acuity of 20/40 or better was attained in 26 of 40 eyes (65%). Because of the low rate of intraoperative complications and the high rate of success, scleral buckling is recommended for most patients with rhegmatogenous retinal detachments associated with severe myopia.

MYOPIA accounts for 12% to 42% of rhegmatogenous retinal detachments, and the risk of retinal detachment increases with an increase in refractive error.¹⁻³

Burton¹ and Winslow and Tasman⁴ found that the retina was successfully reattached in 81% to 86% of eyes with myopia. The use of this technique in the repair of retinal detachments in severely myopic eyes, however, has been

reported to be associated with an increased risk of intraoperative complications.⁵ These complications, which may lead to severe visual loss or blindness, include choroidal or subretinal hemorrhage, choroidal detachment, retinal incarceration, retinal break, postoperative anterior segment ischemia, anisometropia, strabismus, macular distortion, cystoid macular edema, and extrusion or infection of extrascleral implant material.⁵ Therefore, pneumatic retinopexy or primary vitrectomy have been suggested as alternatives to scleral buckling in the management of rhegmatogenous retinal detachment associated with severe myopia.⁶⁻¹⁰

We determined the results and complications of scleral buckling surgery in a consecutive series of patients with rhegmatogenous retinal detachments associated with severe myopia. We arbitrarily defined severe myopia as a refractive error of -5.00 diopters or greater.

Patients and Methods

We performed scleral buckling operations for all patients with rhegmatogenous retinal detachments associated with severe myopia examined at our institution between Jan. 1, 1980, and Dec. 31, 1989. A total of 48 eyes of 46 consecutive patients were operated on, and all the procedures were performed at our institution by four of us (H.L., A.E.K., M.O.Y., or Y.S.). Thus, none of the patients with rhegmatogenous retinal detachments associated with severe myopia examined during the same period of time were operated on with a different technique, such as pneumatic retinopexy or vitrectomy.

Except for eight patients, all were followed up for a minimum of six months. Of these eight patients, two died, and we could not determine their retinal status at the time of death. The other six patients had moved away and could not be located. Our attempts to obtain ocular

Accepted for publication Jan. 25, 1991.

From the Department of Ophthalmology, Jules Stein Eye Institute, UCLA School of Medicine, Los Angeles, California. This study was supported in part by the Charles Kenneth Feldman Fund (Dr. Lewis) and by Research to Prevent Blindness, Inc. (Drs. Rodriguez and Lewis).

Reprint requests to Hilel Lewis, M.D., Jules Stein Eye Institute, 100 Stein Plaza, Los Angeles, CA 90024-7007.

information on these six patients were not successful. Thus, to analyze the long-term results we included only the 40 eyes of 38 patients that were observed for at least six months (mean, 46 months).

The medical and operative records of all patients were reviewed. Drawings and color photographs were also reviewed when available. The following historical data were collected: age; gender; race; previous ocular disease; previous trauma; previous ocular surgery; onset of retinal detachment; and time between the onset of retinal detachment and surgical repair. Ophthalmic data obtained included the following: preoperative and postoperative best-corrected visual acuity; refractive error; status of the lens; intraocular pressure; presence and extent of retinal detachment; number, type, and location of retinal breaks; presence of proliferative vitreoretinopathy; and presence of peripheral retinal abnormalities, such as lattice degeneration or cystic retinal tufts. Intraoperative information obtained included the following: presence and extent of scleral thinning, ectasia, or both; type and extent of the buckling element used; method of chorioretinal adhesion used; need for and location of drainage of subretinal fluid; use of intraocular air or gas; and development of intraoperative complications, such as inadvertent scleral perforation, retinal incarceration, choroidal hemorrhage, or vitreous hemorrhage. The complete medical and operative records were available for all 48 eyes of 46 patients.

Results

The study group included 25 males and 21 females. The ages ranged from 15 to 74 years (mean, 42 years). Thirty-nine patients (85%) were white, five (11%) were Hispanic, and two (4%) were black. The refractive error was between -5.00 and -8.00 diopters in 26 eyes (54%), between -8.25 and -11.25 diopters in 17 eyes (35%), between -11.50 and -14.75 diopters in two eyes (4%), and greater than -15.00 diopters in three eyes (6%). For retinal breaks without a retinal detachment, five eyes (10%) had previous treatment with laser photocoagulation, one eye (2%) with cryoretinopexy, and one eye (2%) with both laser photocoagulation and cryoretinopexy. One patient had previous blunt ocular trauma that was thought to be not related to the retinal detachment.

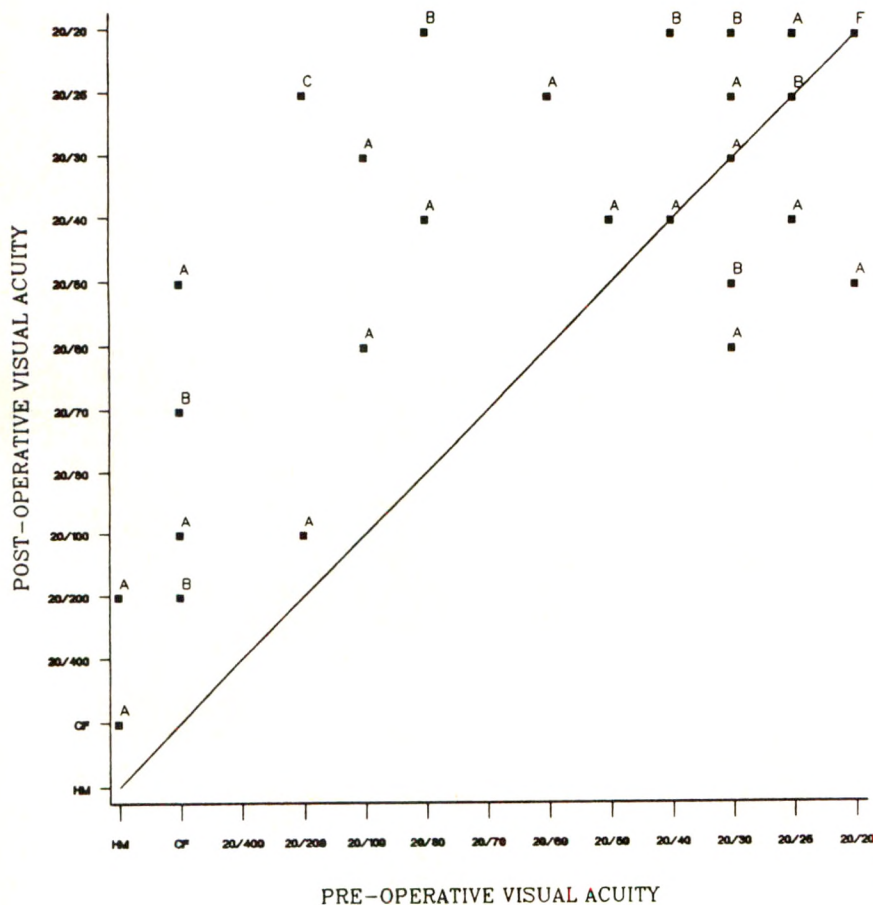
All the eyes were phakic, two had a diagnosis of chronic recurrent uveitis, and none had macular holes. The macula was detached in 15 eyes (31%). Retinal tears were present in 40 eyes (83%), retinal holes in seven eyes (15%), and no retinal breaks could be found in one eye (2%). Lattice degeneration was present in 24 eyes (50%), and the association between retinal tears and lattice degeneration of the retina was observed in 17 eyes (35%). Mild proliferative vitreoretinopathy was present in two eyes (4%). The initial and final visual acuity of the 40 eyes followed up for more than six months are shown in the Figure.

The mean time between diagnosis and scleral buckling was 4½ days. Twenty-four eyes (50%) were operated on in the first 24 hours after the diagnosis was made. Forty eyes were observed from six to 105 months (mean, 46 months), and the remaining eight eyes were observed for five months (two eyes), four months (one eye), three months (one eye), two months (three eyes), and one month (one eye).

The technical variations of the scleral buckling procedures are listed in the Table. Extrascleral implants were performed in 30 eyes (62.5%) and intrascleral implants in 18 eyes (37.5%); cryotherapy was used in 43 eyes (90%) and diathermy in three eyes (6%); and external drainage of subretinal fluid was performed in 37 eyes (77%). Intraocular air was used in four eyes (8%) to increase the intraocular pressure and in two eyes (4%) to tamponade large retinal tears. Balanced salt solution was injected intravitreally in three eyes (6%) to increase the intraocular pressure. In seven eyes (14%) scleral thinning was noted.

Intraoperative complications occurred in four (8%) of the 48 eyes and included retinal incarceration into the drainage site in two eyes (4%), partial choroidal hemorrhage related to the drainage procedure in one eye (2%), and significant choroidal detachment in one eye (2%). No treatment was performed for the retinal incarcerations because they were supported by the scleral buckle. The choroidal hemorrhage and the significant choroidal detachment resolved spontaneously in the postoperative period.

Postoperative complications developed in nine of the 40 eyes (22.5%) that were observed for at least six months and included recurrent retinal detachment in three eyes (7.5%), cystoid macular edema in two eyes (5%), significant choroidal detachments (different from the one noted intraoperatively) in two eyes (5%), macular pucker in one eye (2.5%), and exotropia in



one eye (2.5%). The cause for anatomic failure in the eyes that redetached was the development of new retinal breaks. The two eyes that required injection of air into the vitreous cavity to tamponade large retinal breaks developed new retinal breaks, one located adjacent to the previous break and the other located 60 degrees from the previous retinal tear. All three eyes underwent revision of the scleral buckle, which was successful in two eyes. The third eye required another revision of the scleral buckle.

Of the eight eyes followed up for less than six months, one eye developed cystoid macular edema.

At the last follow-up examination the retinas in all 40 eyes observed for at least six months were totally reattached, and final visual acuity of 20/40 or better was attained in 26 eyes (65%). Twenty-five eyes (62.5%) had better, ten eyes (25%) had the same, and five eyes (12.5%) had worse postoperative visual acuity. There was no correlation between the size or extent of the encircling element and final visual acuity. All five eyes with worse postoperative visual

acuity had final visual acuity of 20/60 or better (Figure). Of the eight eyes followed up for less than six months, visual acuity improved in four eyes, was the same in one, and decreased in three.

Discussion

Using data from the National Health and Nutrition Examination Survey, Sperduto and associates¹¹ found that the prevalence of any degree of myopia in individuals between 12 and 54 years of age was 25% and 24.3% for the right and left eyes, respectively. In the Framingham study, Leibowitz and associates¹² found that in people between ages 52 and 85 years, myopia was present in 17.7%.

Retinal detachment associated with myopia has been found to occur more frequently in middle-aged patients. Cambiaggi¹³ reported that retinal detachment with myopia occurred more often in patients between the ages of 41

TABLE
TECHNICAL VARIATIONS IN SCLERAL BUCKLING
PROCEDURE IN 48 EYES

BAND	TIRE	TYPE OF ELEMENT		EXTENT (GRADES)				TOTAL (%)
		RADIAL (SPONGE)		90	180	270	360	
No	276	No		2	1	—	—	3 (6.2)
No	No	Yes		—	—	—	—	1 (2.0)
240	No	No		—	—	—	2	2 (4.1)
40	220	No		—	—	—	1	1 (2.0)
240	220	No		5	3	—	—	8 (16.6)
240	276	No		5	1	2	—	8 (16.6)
240	280	No		1	1	—	—	2 (4.1)
240	287	No		1	3	—	2	6 (12.5)
240	No	Yes		—	—	—	7	7 (14.5)
No	276	Yes		1	—	—	—	1 (2.0)
240	220	Yes		2	—	—	—	2 (4.1)
240	276	Yes		2	1	1	—	4 (8.3)
240	280	Yes		2	—	—	—	2 (4.1)
240	287	No		—	—	—	1	1 (2.0)

and 70 years. In patients younger than 41 years of age, males were more frequently affected, but there was no significant predilection for either sex in the overall group. Of his patients, 50% had less than -4.00 diopters of myopia. In our patients, the retinal detachment occurred more often between the ages of 30 and 59 years (74%), and there was a slight predilection for males (54%).

Bilateral retinal detachment associated with myopia has been reported.^{13,14} In one study, six of 47 patients (13%) developed a retinal detachment in the fellow eye during 14 years of follow-up (unpublished data, Matthew A. Thomas, M.D., Nov. 11, 1987). Folk and Burton¹⁴ found a significant association between bilateral retinal detachment and myopia (-2.50 diopters or greater). The incidence of myopia in their patients with bilateral retinal detachments was 55% compared to 33% in patients with unilateral retinal detachment, and the incidence of bilateral retinal detachment in the myopic group was 21% compared with 10% in the nonmyopic group. The incidence of bilateral retinal detachment was thought to be related to the combined influences of lattice degeneration of the retina and refractive error and ranged from 8% in the nonmyopic group without lattice degeneration of the retina to 25% in the myopic group with lattice degeneration of the retina. In contrast, the incidence of bilateral retinal detachment in our patients with myopia

was lower (4%), and only one of these two patients had lattice degeneration of the retina.

Byer¹⁵ reported that myopic eyes have an increased incidence of lattice degeneration of the retina. Benson and Morse¹⁶ found that 70% of retinal detachments caused by breaks in areas of lattice degeneration of the retina were myopic. In our series, 50% of the eyes had lattice degeneration of the retina and, of those, 71% had tears associated with the lattice lesions.

In the study by Burton,¹ myopic eyes (greater than -4.00 diopters) accounted for 12% of the rhegmatogenous retinal detachments, and a reduced retinal reattachment rate was found in myopic eyes (86%) when compared with emmetropic eyes (93%).

Winslow and Tasman⁴ found that myopia was the cause of retinal detachment in 28 eyes of 179 children (15%), and 17 of 21 eyes (81%) followed up for at least six months were reattached.

Our results indicate a high anatomic success rate of scleral buckling in the repair of rhegmatogenous retinal detachment associated with severe myopia. All retinas were reattached intraoperatively, and the retinas of 37 of the 40 eyes (92.5%) observed for at least six months were reattached with one operation. With a revision of the scleral buckle, the retinas of two additional eyes were reattached; with a second revision of the scleral buckle, the retina of a third eye was reattached. Final visual acuity of 20/40 or better was attained in 26 of the 40 eyes (65%) followed up for at least six months. We believe that the good visual results obtained may be because of the large number of eyes that had retinal detachment and an attached macula (69%) as well as because of early repair of the retinal detachments (50% of eyes operated on within 24 hours of diagnosis).

An important consideration in the treatment of retinal detachments in myopic eyes is the technical difficulty encountered. In this regard, the refractive error itself is not as important as the effect of myopia on the ocular tissues, such as elongation of the globe, scleral thinning, liquefaction of the vitreous, and the complex vitreoretinal relationships that are often present. These changes produce special problems in achieving the goals of scleral buckling.¹⁰ Because of the anatomic peculiarities of severely myopic eyes, intraoperative complications may be more frequent. Surgical exposure of large myopic eyes may be difficult because the size of the globe limits rotation and posterior expo-

sure. Also, retinal breaks tend to be large, multiple, or posterior and may be impossible to close with a scleral buckle because of the difficulty in exposure and scleral thinning. Because of thinned and perhaps more fragile choroidal tissue, drainage of subretinal fluid with the inevitable rapid ocular decompression that follows may have a higher risk of producing a choroidal hemorrhage. Similarly, extensive choroidal detachment may occur.⁵

Intrascleral suture placement in eyes with thin sclera or with staphylomata is difficult, and eye-wall perforation with a needle may lead to hemorrhage, retinal perforation, or inopportune decompression of the globe from drainage of vitreous or subretinal fluid. In our series of 46 patients (48 eyes), the frequency of intraoperative complications was low; however, only 12 of 48 eyes (25%) had myopia greater than 10.00 diopters. One eye (2%) developed choroidal hemorrhage, one eye (2%) developed a significant choroidal detachment, and in another two eyes (4%) the retina was incarcerated in the drainage site.

In the postoperative period three eyes (7.5%) of the 38 patients (40 eyes) observed for at least six months developed a recurrent retinal detachment caused by the development of new retinal breaks. Two of the three eyes that developed new retinal breaks had air injected into the vitreous cavity at the time of surgery. Two eyes underwent a successful revision of the scleral buckle, and a third eye required a second revision of the scleral buckle. Two eyes (5%) developed significant choroidal detachments, but both cases resolved spontaneously. Other postoperative complications included cystoid macular edema in two eyes (5%), macular pucker in one eye (2.5%), and exotropia in one eye (2.5%). Extrusion, intrusion, or infection of the scleral buckle material did not occur in any of our patients.

Pneumatic retinopexy or primary vitrectomy have been suggested as alternative procedures in the treatment of retinal detachments associated with myopia.⁶⁻¹⁰ The main advantages cited in favor of these procedures as compared to scleral buckling include a possible lower risk of intraoperative complications, a reduction in postoperative discomfort, and avoidance of motility problems and refractive changes. Because of differences in reports of surgical experience, it is difficult to find comparable series of patients with severe myopia treated with pneumatic procedures alone. McAllister and associates⁷ compared the success rate and com-

plications of treating uncomplicated retinal detachments with single or multiple breaks within the superior 240 degrees of the fundus by pneumatic retinopexy, Lincoff balloon, or scleral buckle. Although their group included patients with myopia (greater than -4.00 diopters), they did not specifically note the results in this particular subgroup. Algvere, Hallnäs, and Palmqvist⁶ reported 58 consecutive eyes with rhegmatogenous retinal detachment treated with pneumatic retinopexy. This technique successfully reattached the retina in 18 of 22 (82%) myopic eyes (-3.00 to -11.00 diopters). This is a lower rate of anatomic success for a single intervention when compared with our results, namely 37 of 40 eyes (92.5%) observed longer than six months. Van Effenterre and associates⁸ reported the anatomic success in treating retinal detachments in 120 eyes, some of which were myopic, by either cryotherapy, vitrectomy, and gas injection or cryotherapy and gas injection only. Total retinal reattachment with one intervention was 82% and 85%, respectively, but the results were not reported according to the refractive status of the eye.

The potential complications of pneumatic retinopexy also need to be considered. The intraocular gas bubble may increase vitreous traction and cause further tears, mainly 180 degrees opposite to the bubble.¹⁷ The absence of support at the vitreous base makes postoperative retinal tears more likely to cause a recurrent retinal detachment. Migration of gas through retinal breaks to the subretinal space has been reported¹⁸ and may be more likely in severely myopic eyes with large retinal breaks. Endophthalmitis is rare, but if it occurs it frequently leads to severe visual loss.

Finally, the role of vitrectomy surgery as a primary procedure in severely myopic eyes is controversial.^{9,10} The main advantages of repairing retinal detachments in myopic eyes with vitrectomy as compared with scleral buckle include little or no scleral manipulation in patients with extremely thin sclera, complete reattachment of the retina without the risk of gaping of the retinal break over the posterior edge of the scleral buckle, and the technical ease with which fluid-air exchange and internal drainage of subretinal fluid achieves internal tamponade in eyes with multiple, large, or posterior breaks. Conversely, potential disadvantages of vitrectomy alone as the primary procedure include the absence of a scleral buckle to support retinal breaks and offset some degree of periretinal traction or postoperative

vitreoretinal traction, as well as the complications of the procedure, such as uveal effusion, subretinal infusion, peripheral retinal dialysis, or new retinal tears, lens damage, incarceration of the vitreous or the retina in the sclerotomy site, intraoperative hemorrhage, endophthalmitis, and sympathetic ophthalmia. Moreover, there is a higher risk of developing nuclear cataract.¹⁰ Nevertheless, in certain eyes in which the technical problems of scleral buckling are great (thin sclera, large, multiple, or posterior retinal breaks), vitrectomy may be preferable to scleral buckling.

Although we cannot compare our results using scleral buckling with either pneumatic retinopexy or vitrectomy, because neither of these two procedures were performed in our patients with rhegmatogenous retinal detachments and severe myopia, the high rate of success and the low risk of surgical complications suggest that scleral buckling is an excellent treatment for most patients with retinal detachment associated with severe myopia.

References

1. Burton, T. C.: Preoperative factors influencing anatomic success rates following retinal detachment surgery. *Trans. Am. Acad. Ophthalmol. Otolaryngol.* 83:499, 1977.
2. Schepens, C. L., and Marden, D.: Data on the natural history of retinal detachment. Further characterization of certain unilateral nontraumatic cases. *Am. J. Ophthalmol.* 61:213, 1966.
3. Ashrafzadeh, M. T., Schepens, C. L., Elzeneiny, I. I., Moura, R., Morse, P., and Kraushar, M. F.: Aphakic and phakic retinal detachment. I. Preoperative findings. *Arch. Ophthalmol.* 89:476, 1973.
4. Winslow, R. L., and Tasman, W.: Juvenile rhegmatogenous retinal detachment. *Ophthalmology* 85:607, 1978.
5. Schepens, C. L.: *Retinal Detachment and Allied Diseases*, vol. 2. Philadelphia, W. B. Saunders, 1983, pp. 589-597.
6. Algvere, P., Hallnäs, K., and Palmqvist, B.-M.: Success and complications of pneumatic retinopexy. *Am. J. Ophthalmol.* 106:400, 1988.
7. McAllister, I. L., Meyers, S. M., Zegarra, H., Gutman, F. A., Zakov, Z. N., and Beck, G. J.: Comparison of pneumatic retinopexy with alternative surgical techniques. *Ophthalmology* 95:877, 1988.
8. Van Effenterre, G., Haut, J., Larriart, P., Abid-Rached, J., and Vachet, J. M.: Gas tamponade as a single technique in the treatment of retinal detachment. Is vitrectomy needed? A comparative study of 120 cases. *Graefes Arch. Clin. Exp. Ophthalmol.* 225:254, 1987.
9. Charles, S.: Vitrectomy in high myopia. In Thompson, F. B. (ed.): *Myopia Surgery. Anterior and Posterior Segments*. New York, Macmillan Publishing Co., 1990, pp. 209-238.
10. Kreiger, A. E.: Retinal detachment. In Thompson, F. B. (ed.): *Myopia Surgery. Anterior and Posterior Segments*. New York, Macmillan Publishing Co., 1990, pp. 239-266.
11. Sperduto, R. D., Seigel, D., Roberts, J., and Rowland, M.: Prevalence of myopia in the United States. *Arch. Ophthalmol.* 101:405, 1983.
12. Leibowitz, H. M., Krueger, D. E., Maunder, L. R., Milton, R. C., Kini, M. M., Kahn, H. A., Nickerson, R. J., Pool, J., Colton, T. L., Ganley, J. P., Lowenstein, J. I., and Dawber, T. R.: The Framingham Eye Study monograph. *Surv. Ophthalmol.* 24:335, 1980.
13. Cambiaggi, A.: Myopia and retinal detachment. *Am. J. Ophthalmol.* 58:642, 1964.
14. Folk, J. C., and Burton, T. C.: Bilateral phakic retinal detachment. *Ophthalmology* 89:815, 1982.
15. Byer, N. E.: Clinical study of lattice degeneration of the retina. *Trans. Am. Acad. Ophthalmol. Otolaryngol.* 69:1064, 1965.
16. Benson, W. E., and Morse, P. H.: The prognosis of retinal detachment due to lattice degeneration. *Ann. Ophthalmol.* 10:1197, 1978.
17. Dreyer, R. F.: Sequential retinal tears attributed to intraocular gas. *Am. J. Ophthalmol.* 102:276, 1986.
18. McDonald, H. R., Abrams, G. W., Irvine, A. R., Sipperly, J. O., Boyden, B. S., Fiore, J. V., and Zegarra, H.: The management of subretinal gas following attempted pneumatic retinopexy. *Ophthalmology* 94:319, 1987.

Current Practices in the Management of Ocular Toxoplasmosis

Robert E. Engstrom, Jr., M.D., Gary N. Holland, M.D., Robert B. Nussenblatt, M.D.,
and Douglas A. Jabs, M.D.

To determine current practices in the management of ocular toxoplasmosis, 72 of 85 uveitis specialists (85%) in the American Uveitis Society completed a detailed questionnaire. Questions involved the indications for beginning treatment, choice of antiparasitic/antimicrobial agents, and experience with treatment of ocular toxoplasmosis in special situations including pregnancy, neonatal infections, and immunocompromised patients.

Most of the respondents treat patients whose visual acuity had decreased to worse than 20/200, lesions located in the peripapillary, perifoveal, or maculopapillary bundle regions, and lesions associated with severe vitreous inflammation. Most would not treat patients who retained visual acuity of 20/20, lesions located in the far peripheral retina, or lesions associated with only trace to mild vitreous inflammation. Treatment of other combinations of factors remains controversial.

Eight different antimicrobial drugs are used in various combinations for lesions threatening the macula or optic nerve head. Systemic corticosteroids are used by 59 of 62 respondents (95%) as part of their initial treatment regimen. The most commonly used regimens

are pyrimethamine/sulfadiazine/corticosteroids (20 of 62 [32%]) and pyrimethamine/sulfadiazine/clindamycin/corticosteroids (17 of 62 [27%]). Adjunctive therapies (photocoagulation, cryotherapy, or vitrectomy) have been used by 20 of 60 respondents (33%). Most alter treatment during pregnancy, in newborn patients, and in patients with the acquired immunodeficiency syndrome.

TOXOPLASMA GONDII is the most common cause of infectious retinochoroiditis in otherwise healthy individuals.¹ Although the combination of pyrimethamine and sulfadiazine has been recommended for many years as a treatment for ocular toxoplasmosis,^{2,3} the few prospective, randomized clinical studies designed to assess the effectiveness of this combination have provided conflicting results.⁴⁻⁶ A number of other drugs have demonstrated in vitro and in vivo efficacy against *T. gondii*, but their role in the treatment of human ocular toxoplasmosis remains uncertain. The best treatment for patients with ocular toxoplasmosis in special circumstances, such as the immunocompromised patient or the pregnant patient, remains even less clearly defined. Nonmedical therapies, including laser photocoagulation,^{7,8} cryotherapy,⁹ or vitrectomy,¹⁰ have also been recommended by some for the treatment of acute lesions.

To gain a better understanding of current treatment practices for ocular toxoplasmosis, a detailed questionnaire was sent to physician members of the American Uveitis Society. The Society comprises physicians and other vision scientists with a special interest in ocular inflammation. For membership in the American Uveitis Society, ophthalmologists must have had fellowship training in uveitis or have been in practice for at least three years after residency training, with 25% of their patient-care time spent in the treatment of patients with intraocular inflammation.

Accepted for publication Jan. 30, 1991.

From the UCLA Ocular Inflammatory Disease Center, Jules Stein Eye Institute, and Department of Ophthalmology, UCLA School of Medicine, Los Angeles, California (Drs. Engstrom and Holland); National Eye Institute, National Institutes of Health, Bethesda, Maryland (Dr. Nussenblatt); and Wilmer Ophthalmological Institute, Johns Hopkins University and Hospital, Baltimore, Maryland (Dr. Jabs). This study was a project of the Education and Research Committee, American Uveitis Society. This study was supported in part by Research to Prevent Blindness, Inc. (Dr. Holland).

Reprint requests to Gary N. Holland, M.D., Jules Stein Eye Institute, 100 Stein Plaza, UCLA, Los Angeles, CA 90024-7003.

The questionnaire addressed three major categories of toxoplasmosis management: indications for beginning treatment; management practices for typical patients (that is, immunocompetent adult male or nonpregnant female patients with a recurrent, vision-threatening macular lesion and a decrease in vision but without foveal destruction and therefore good potential for full visual recovery with successful therapy); and management of active disease in pregnant, newborn, or immunocompromised patients.

Material and Methods

Members were asked to estimate the number of patients with active ocular toxoplasmosis whom they examine each year. If the number of patients seen was provided as a range, the mean of the upper and lower values was used to estimate the number of patients seen each year by that respondent. Only those members who have treated patients with ocular toxoplasmosis were asked to complete the questionnaire.

Members were asked whether they treated all cases of typical ocular toxoplasmosis as defined regardless of the ocular findings. If members did not treat every case, they were asked to identify factors that might influence their decision to treat in five categories: changes in visual acuity; lesion location; lesion size; the type of lesion; and the amount of associated vitreous inflammatory reaction. They were then asked whether that factor was an absolute indication (would always treat when the factor was present), a relative indication (would be more likely to treat when the factor was present but would not treat based on the factor alone), a relative contraindication (would be less likely to treat when the factor was present but would not prevent beginning treatment in every case), an absolute contraindication (would never treat when the factor was present), or an irrelevant factor (presence of factor would have no role on decision to treat).

Specific factors were provided for each category considered. Changes in visual acuity were divided into the following: retention of 20/20 visual acuity; decrease in visual acuity to 20/40; and decrease in visual acuity to worse than 20/200. Lesion location was identified by retinal zones previously described in a study of necrotizing retinal infections.¹¹ Retinal zones and subdivisions included the following: Zone

1, considered to be that portion of the retina where infection is immediately sight-threatening and corresponding to an area extending 3,000 μm (2 disk diameters) from the fovea (approximately that area enclosed by the major temporal vascular arcades) or 1,500 μm from the margins of the optic nerve head; Zone 2, extending anterior from Zone 1 to the clinical equator of the eye, identified by the anterior borders of the ampullae of the vortex veins (the farthest anterior extent of the retina that can be photographed easily); and Zone 3, extending anterior from Zone 2 to the ora serrata. Zone 1 was further divided into peripapillary, maculopapillary bundle, and perifoveal areas. Lesion size was divided into areas less than or equal to 1 disk diameter or greater than 1 disk diameter. Potentially important lesion characteristics listed on the questionnaire included the following: single, recurrent satellite; multifocal; punctate outer retinal toxoplasmosis; acquired lesions; and lesions persisting for more than one month regardless of size or location. Vitreous reaction was scored on a scale of severity from trace through mild, moderate, marked, and severe, based on the scale described by Nussenblatt and associates.¹² (These descriptive terms correspond to their numeric scale as follows: mild, 1+; moderate, 2+; marked, 3+; and severe, 4+.) The motivation of respondents for choosing various indications was not solicited in the questionnaire.

Questions regarding treatment addressed the following: preferred antimicrobial therapy for a typical case; management of drug-related toxicity; use of corticosteroids (including topical, periocular, and oral routes of administration); experience with investigational agents; and use of adjunctive therapies, such as laser photocoagulation, cryotherapy, or vitrectomy. Members were also asked to describe lesion-associated factors for which they would modify their standard therapeutic regimen.

To determine whether members alter their management in special situations, they were asked to describe how they treat pregnant patients, neonatal patients, and immunosuppressed patients with ocular toxoplasmosis. With regard to pregnant patients, they were asked about indications and drug therapy, whether they treat acquired maternal disease specifically to protect the fetus, and if they treat recurrent ocular disease in the woman to preserve vision. Members were asked to describe the ways in which their treatment of newborns with active toxoplasmosis differed, if at all, from that

of adult patients. Questions pertaining to the treatment of the immunocompromised patient dealt with whether their indications for treatment, the drugs used, and patient follow-up differed from that for an immunocompetent patient.

For each question in which various factors were listed as responses in a multiple-choice format (for example, indications for treatment), members were also allowed to answer with information other than those factors already listed.

Results

Completed questionnaires were returned by 72 of the 85 physician members (85%) of the American Uveitis Society. Of the respondents, ten (14%) stated that they either do not examine patients or have not had patients with active ocular toxoplasmosis in their practices. The remaining 62 respondents (86%) reported examining a median of ten patients with ocular toxoplasmosis (range, two to 75 patients) per year. The results are based on the responses of these 62 respondents.

Some respondents did not answer every question. Numeric data reflect the actual number of respondents answering any individual question and are reported as the number of respondents answering yes to a question or choosing a given response in a multiple-choice question and the total number answering that question, followed by the corresponding percentage.

Indications for treatment—Of the 62 physicians who reported having patients with active ocular toxoplasmosis in their practice, four (6%) treat all active cases regardless of the ocular findings. For the remaining respondents, disease-associated factors that are considered to be absolute or relative indications for therapy by at least 20% are listed in Table 1. Factors considered to be absolute or relative contraindications for therapy by at least 20% are listed in Table 2.

Visual acuity—Any decrease in vision from baseline is considered an indication for treatment by 38 of 52 (75%) respondents. The percentage who consider decreased vision an absolute indication, regardless of other findings, increases with the severity of visual loss, with 34 of 56 (61%) considering visual acuity worse than 20/200 as an absolute indication for treatment. In contrast, 32 of 53 (60%) believe that

retention of 20/20 visual acuity is a relative contraindication to treatment.

Lesion location and size—Of 58 respondents, most treat lesions located anywhere within Zone 1, regardless of other factors: 45 (78%) for peripapillary lesions; 54 (93%) for maculopapillary bundle lesions; and 57 (98%) for perifoveal lesions. There was no consensus regarding treatment of Zone 2 lesions; this location is considered a relative indication by 26 of 53 (49%), a relative contraindication by 19 of 53 (36%), and an irrelevant factor by eight of 53 (15%). Location in Zone 3, however, is believed by 33 of 52 (63%) to be a relative contraindication to treatment.

Of 56 respondents, 34 (63%) consider lesion size larger than 1 disk diameter an indication for treatment; seven (13%) consider it an absolute indication for treatment. Twenty-seven of 53 (51%) consider lesion size less than 1 disk diameter an irrelevant factor in their decision to treat. Nine of 53 (17%) consider small lesions a relative contraindication to treatment.

Other lesion characteristics—Most (30 of 55, 55%) consider the presence of active retinal lesions in acquired disease (as opposed to recurrent ocular toxoplasmosis) to be an indication for treatment, but only 11 of 55 (20%) consider it an absolute indication. The presence of multiple active lesions are believed by 29 of 56 (52%) to be an indication for treatment; nine of 56 (16%) consider multifocal disease an absolute indication.

A consensus did not exist regarding treatment of punctate outer retinal toxoplasmosis. It was considered a relative indication by 23 of 51 (45%), an irrelevant factor by 17 of 51 (33%), and a relative contraindication by nine of 51 (18%).

Persistence of disease activity for more than one month, regardless of other lesion characteristics, is considered an indication for initiation of treatment by most respondents (43 of 58, 74%), with 12% considering it an absolute indication (seven of 58, 12%).

Vitreous inflammation—Vitreous inflammatory reaction is considered an indication for treatment by most of the respondents only when it is greater than moderate in severity. Fifty-six of 57 (98%) consider severe vitreous reaction an indication for treatment; 36 of 57 (63%) consider this level of reaction an absolute indication.

Antimicrobial agents—Eight different antimicrobial agents (pyrimethamine, sulfadiazine, clindamycin, sulfisoxazole, sulfadiazine/sulfamerazine/sulfamethazine, trimethoprim/sul-



TABLE 1
FACTORS SUGGESTING THAT OCULAR
TOXOPLASMOSIS SHOULD BE TREATED

FACTOR*	NO. OF RESPONDENTS IN AGREEMENT/ TOTAL NO. OF RESPONDENTS (%)	NO. OF RESPONDENTS WHO CONSIDER FACTOR AN ABSOLUTE INDICATION/TOTAL NO. OF RESPONDENTS (%)
Visual acuity		
Any decrease in visual acuity	38/52 (75)	1/52 (02)
Visual acuity below 20/40	49/57 (86)	12/57 (21)
Visual acuity below 20/200	55/56 (98)	34/56 (61)
Lesion location		
Zone 1, peripapillary	58/58 (100)	45/58 (80)
Zone 1, maculopapillary bundle	58/58 (100)	54/58 (93)
Zone 1, perifoveal	58/58 (100)	57/58 (98)
Lesion size		
≤ 1 disk diameter	17/53 (32)	2/53 (04)
> 1 disk diameter	34/57 (60)	7/57 (12)
Vitreous reaction		
Trace	12/57 (21)	0/57 (00)
Mild	15/57 (26)	2/57 (04)
Moderate	34/56 (61)	6/56 (11)
Marked	49/57 (86)	23/57 (40)
Severe	56/57 (98)	36/57 (63)
Type of active lesion		
Single, recurrent satellite	23/55 (42)	1/55 (02)
Multifocal infection	38/56 (68)	9/56 (16)
Punctate outer retinal lesions	25/51 (49)	2/51 (04)
Acquired infection	30/55 (55)	11/55 (20)
Persistence > 1 month	43/58 (74)	7/58 (12)

*Factors identified by at least 20% of respondents as an absolute or relative indication for treatment.

famethoxazole, minocycline, and tetracycline) both with and without corticosteroids are combined in 15 different regimens as the treatment of choice for ocular toxoplasmosis (Table 3).

Sulfonamides are used by 56 of the 62 respondents (90%). Sulfadiazine is the most commonly used agent (51 of 62, 82%). A sulfonamide is used with pyrimethamine by 43 of 62 (69%) in various regimens. Clindamycin is used by 34 of 62 (55%) respondents.

The combination of pyrimethamine, sulfadiazine, and corticosteroids is used by 20 of 62

(32%). Clindamycin is used with these three agents (quadruple therapy) as treatment of choice by 17 of 62 (27%). A combined regimen of sulfadiazine, clindamycin, and corticosteroids is used by ten of 62 (16%). Clindamycin and corticosteroids are used by four of 62 (6%) (Table 4). All other combinations are used by only one respondent each.

Of those respondents who use pyrimethamine, 37 of 42 (88%) administer a loading dose, ranging from 50 mg given once to 100 to 200 mg given for one or two days. The most frequently used loading dose is 75 to 100 mg given in one day and divided into three or four doses (23 of 37, 62%). Subsequent treatment is administered as either 25 mg daily (19 of 41, 47%) or 50 mg daily (19 of 41, 47%). Duration of pyrimethamine therapy is usually four to six weeks (range, one to eight weeks). Most adjust the duration of therapy based on the clinical response.

Nearly all respondents who use pyrimethamine also administer folinic acid to prevent hematologic toxicity (51 of 52, 98%). The tablet form of folinic acid is used by 31 of 52 (60%), with 5 mg given three times a week being the most commonly used dose. The remainder (21 of 52, 40%) administer the intravenous preparation of folinic acid orally as one vial (3 mg) either two or three times per week.

Laboratory testing is performed routinely by nearly all respondents to monitor for development of leukopenia and thrombocytopenia. Most check laboratory variables weekly and discontinue therapy for a white blood cell count less than 4,000 cells/mm³ or a platelet count less than 100,000/mm³.

Of respondents who use pyrimethamine as a drug of first choice and encounter adverse reactions restricting its use, 29 of 38 (76%) substitute clindamycin while continuing other agents. Two of 38 (5%) use spiramycin, one of 38 (3%) tetracycline, and one of 38 (3%) minocycline. Six of 38 (16%) discontinue pyrimethamine without adding a replacement agent.

Sulfadiazine is administered as a 1-g dose given four times daily for four to six weeks by 38 of 43 (88%). An initial loading dose of 2 to 4 g in one administration is given by 23 of 37 respondents (62%). When toxicity to sulfadiazine is encountered, 30 of 46 (65%) substitute clindamycin while continuing other agents. Other less frequently used alternative agents include minocycline (five of 46, 11%) and tetracycline (four of 46, 9%). Seven of 46 (15%)

TABLE 2
FACTORS SUGGESTING THAT OCULAR
TOXOPLASMOSIS DOES NOT NEED TREATMENT

FACTOR*	NO. OF RESPONDENTS IN AGREEMENT/TOTAL NO. OF RESPONDENTS (%)	NO. OF RESPONDENTS WHO CONSIDER FACTOR AN ABSOLUTE CONTRAINDICATION/ TOTAL NO. OF RESPONDENTS (%)
Visual acuity		
20/20	36/58 (68)	4/58 (7)
Lesion location		
Zone 2	19/53 (36)	0/53 (0)
Zone 3	34/52 (65)	1/52 (2)
Vitreous inflammatory reaction		
Trace	24/56 (43)	0/56 (0)
Mild	23/57 (40)	1/57 (2)

*Factors identified by at least 20% of respondents as a relative or absolute contraindication for treatment.

discontinue sulfadiazine without adding a replacement agent.

Clindamycin is administered in a 300-mg dose given four times daily for three to six weeks by 31 of 34 respondents (91%).

Spiramycin has been used by only three of 62 respondents (5%). Two of the three respondents use spiramycin for slowly healing lesions only after patients have received sequential six-week courses of combination pyrimethamine/sulfadiazine therapy and clindamycin therapy. Spiramycin is then administered for up to two years after the acute episode. The other respondent has used spiramycin as a sulfonamide alternative in a patient with known sulfonamide allergy.

Corticosteroids—Only 16 of 59 respondents use topical corticosteroids to treat any anterior chamber inflammatory reaction associated with toxoplasmic retinochoroiditis. The rest base their use of topical corticosteroids on the severity of the reaction and its associated complications and symptoms. All respondents use topical corticosteroids for anterior chamber inflammation if synechiae have formed, and most treat for redness and discomfort (48 of 59, 81%).

Periocular corticosteroids have been used by 16 of 61 (26%) respondents, but 15 of these 16 (94%) have done so only with concurrent antiparasitic therapy. Common indications are in-

tolerance or contraindications to oral corticosteroid use (six of 16, 38%) or severe vitreous inflammation (four of 16, 25%). Other indications include macular or peripapillary lesions, presence of hypopyon, or patient noncompliance to oral therapy. Eight of 16 (50%) use 40 mg of triamcinolone acetonide, and five of 16 (31%) use 40 mg of methylprednisolone given once or twice, with favorable outcomes reported by nine of 12 respondents (75%). Of the 12 respondents providing outcomes of therapy, only one reported worsening of disease.

Oral corticosteroids are used by 56 of 57 respondents (98%) for active lesions threatening the macula or optic nerve head. Thirty-eight of 53 (72%) also use oral corticosteroids for lesions causing a decrease in vision, whereas only seven of 54 (13%) give oral corticosteroids based only on the presence of a vitreitis. Oral corticosteroids as single therapy have been used by four of 56 (7%). Indications cited for use of corticosteroids as the only agent included the need to treat patients intolerant to both pyrimethamine and sulfadiazine. No adverse reactions were reported by the respondents.

Corticosteroids are begun simultaneously with antiparasitic agents by 29 of 58 (50%), whereas the remaining 29 initiate corticosteroid therapy only after 24 to 48 hours of antiparasitic therapy. Thirty-seven of 46 (80%) discontinue corticosteroids on the basis of clinical response, whereas the remaining nine (20%) only administer corticosteroids during the first one to three weeks of therapy.

Adjunctive therapies—Laser photocoagulation, cryotherapy, or vitrectomy have been used for active ocular toxoplasmosis by one third of the respondents (20 of 60, 33%) with seven of 60 (12%) having used more than one modality. Laser photocoagulation has been used by eight of 60 (13%) respondents either for sight-threatening lesions, intolerance to oral medications, persistence of lesions for longer than one year, or during pregnancy. Treatment outcomes were described as generally favorable. Cryotherapy has been used by six of 60 (10%) respondents primarily for patients with chronic, peripheral lesions and contraindications to antiparasitic drugs. Rapid resolution after cryotherapy was reported by three respondents, whereas slow resolution was reported by two respondents. Vitrectomy has been used by five of 60 (8%) for treating active inflammation. Of the three respondents providing outcomes, two reported

TABLE 3
AGENTS USED IN THE TREATMENT OF OCULAR TOXOPLASMOSIS

AGENT*	USUAL DOSAGE†
Dihydrofolate reductase inhibitors	
Pyrimethamine	75–100 mg loading dose given over 24 hours, followed by 25–50 mg daily for 4–6 weeks
Trimethoprim/sulfamethoxazole	One tablet given twice daily for 4–6 weeks
Sulfonamides	
Sulfadiazine	2.0–4.0 g loading dose initially, followed by 1.0 g given four times daily for 4–6 weeks
Sulfadiazine/sulfamerazine/sulfamethazine	2.0–4.0 g loading dose initially, followed by 1.0 g given four times daily for 4–6 weeks
Sulfisoxazole	2.0 g loading dose initially, followed by 1.0 g given four times daily for 4–6 weeks
Tetracyclines	
Tetracycline	2.0 g load over 24 hours, then 250 mg given four times daily for 4–6 weeks
Minocycline	100 mg given once or twice daily for 4–6 weeks
Other antimicrobial agents	
Clindamycin	300 mg given four times daily for 3–6 weeks
Other drugs	
Folinic acid	5.0 mg tablet or 3 mg intravenous preparation given orally, two to three times weekly for duration of pyrimethamine therapy
Prednisone	40–60 mg daily for 2–6 weeks depending on clinical response; taper off before discontinuing antimicrobial therapy

*Drug used by at least one respondent as part of initial therapy for typical toxoplasmic lesions.

†Most frequently cited dosage by those using each drug as part of their initial therapy for typical toxoplasmic lesions.

excellent results with the other reporting decreased visual acuity, marked retinal traction, and subretinal fluid collection.

Special situations—Pregnancy: Active ocular toxoplasmosis in pregnant women has been treated by 22 of 57 respondents (39%). Of these, only six (27%) have treated the woman with the goal of protecting the fetus from infection, whereas all will treat the woman to preserve vision. Eighteen of 22 (82%) have the same indications for beginning treatment as for the nonpregnant patient, whereas three (14%) will only treat when lesions are located in Zone 1. Sixteen of 21 (76%) alter therapy during pregnancy. Sulfadiazine is the most commonly used drug (ten of 16, 63%), either as single therapy (three of 16, 19%) or in combination with corticosteroids (three of 16, 19%), with clindamycin (three of 16, 19%), or with pyrimethamine (one of 16, 6%). Pyrimethamine, either alone or in combination with other agents, is used by four of 21 (19%) during pregnancy. Spiramycin has been used by two of 16 (13%) respondents for treatment of the pregnant patient.

Neonatal disease: Only four of 57 respon-

dents (7%) have treated neonatal patients with active ocular disease. All four respondents treat every patient regardless of findings. Two use a combination of pyrimethamine and sulfadiazine for six weeks, followed by spiramycin therapy for eight weeks; this cycle is repeated three times with two-month intervals of no therapy between cycles. The remaining two respondents administer the same drugs as those used for adults but with adjusted doses.

Immunocompromised patients: Active ocular toxoplasmosis has been treated in patients who are immunocompromised by 38 of 56 respondents (68%). Of the conditions responsible for immunosuppression, human immunodeficiency virus-associated disease is the most common, with other causes including organ transplantation and autoimmune disorders. Twenty of 35 (57%) have the same indications for beginning treatment as in immunocompetent patients. Of those modifying their indications for treatment, 11 of 15 (73%) treat all lesions in these patients. Drug therapy is altered by five of 38 (13%), most frequently by excluding both pyrimethamine and corticosteroids. Continued administration of drugs (maintenance therapy)

TABLE 4
PREFERRED THERAPEUTIC REGIMENS FOR TYPICAL
CASES OF OCULAR TOXOPLASMOSIS*

REGIMEN†	RESPONDENTS
	NO. (%)
Pyrimethamine/folinic acid, sulfadiazine, prednisone	20 (32)
Pyrimethamine/folinic acid, sulfadiazine, clindamycin, prednisone‡	17 (27)
Sulfadiazine, clindamycin, prednisone	10 (16)
Clindamycin, prednisone	4 (06)

*A typical case was defined as an immunocompetent male or nonpregnant female patient with a lesion threatening the macula or optic nerve head, who has decreased vision but potential for full recovery of central vision.

†All drug combinations cited by more than one respondent.

‡Referred to by some investigators as quadruple therapy.

for the duration of the immunocompromised state is provided by 24 of 38 (63%), whereas the remainder treat only while lesions are active. Monitoring of these patients is performed differently by 20 of 38 (53%), usually in the form of more frequent follow-up.

Discussion

Toxoplasma gondii has been recognized as a human ocular pathogen for nearly 50 years, but the best treatment for this infection remains a subject of controversy. The synergistic combination of pyrimethamine and sulfadiazine was first recommended by Eyles and Coleman^{3,13} in 1953. In the ensuing years, other reports have provided conflicting data and recommendations regarding the management of ocular toxoplasmosis. Consequently, a variety of therapeutic regimens are used. In this study we attempted to identify variations in the management of ocular toxoplasmosis as currently practiced by uveitis specialists.

Few treat every case of active ocular toxoplasmosis regardless of lesion characteristics. Most modify their therapy for the individual patient. Visual impairment and the potential for visual loss are considered to be the most important factors in determining whether to begin treatment. Treatment is usually begun when lesions

cause a sudden decrease in vision. The proportion who treat, based on vision alone, increases with increasing severity of visual loss. Most also begin treatment if the lesion, by virtue of its location in relation to the fovea or optic nerve head, has the potential for causing permanent visual impairment. Lesions less likely to affect vision (those located peripherally and those associated with minimal vitreous reaction) are usually observed without treatment. Lesion size alone is considered less important in management decisions, presumably because size is less important than location for visual impairment. A large peripheral lesion, for example, will affect vision less than a small perifoveal lesion. Nevertheless, 34 of 57 respondents (60%) still consider lesions greater than 1 disk diameter to be at least a relative indication for treatment.

The natural course of solitary lesions occurring at the margin of a healed scar or single satellite lesions that are removed from a retinochoroidal scar is generally accepted as self limited. When considering lesion characteristics alone, most respondents are less likely to treat single, recurrent lesions.

Only half of the respondents consider punctate outer retinal toxoplasmosis lesions a relative indication for treatment, perhaps because these lesions are not typically associated with vitreous inflammation.^{14,15} Despite the absence of inflammation with these lesions, their natural course and their potential for retinal destruction appear to be similar to more typical ocular toxoplasmosis lesions. Other atypical lesions whose natural course is perhaps less understood or that may indicate a more severe infection, such as multifocal lesions, acquired lesions, and lesions persisting for more than one month, are generally considered an indication for treatment.

A number of antimicrobial/antiparasitic agents have demonstrated either in vitro or in vivo efficacy against *T. gondii*, including pyrimethamine,¹⁶ various sulfonamides (sulfadiazine,¹⁷ sulfamerazine,¹⁷ sulfamethazine,¹⁷ and sulfapyrazine¹⁸), clindamycin,¹⁹ and tetracyclines.²⁰ Eight different antimicrobial agents are used with or without corticosteroids in 15 different regimens as initial therapy for ocular toxoplasmosis. Of these, 51 of 62 respondents (82%) use one of only four different regimens. Regimens consisting of multiple drugs were cited by most, with 53 of 62 respondents (85%) using either three or four agents. This practice

may reflect a perception that lesions respond incompletely to any given agent.

There is less evidence in published reports that clindamycin is as effective for treatment of ocular toxoplasmosis as pyrimethamine or sulfadiazine, but it is used by more than half of the respondents as part of their initial therapy. Clindamycin is also the most frequent choice for alternative therapy when toxicity to either pyrimethamine or sulfadiazine is encountered. Interest among ophthalmologists in the use of clindamycin is probably because the drug appears to be concentrated in ocular tissue and can penetrate cyst walls.²¹ Animal experiments have shown that clindamycin treatment reduces the number of, although it does not eliminate, tissue cysts,²² but there is no good clinical evidence to support the concept that clindamycin prevents recurrences.²³

Retinal necrosis caused by *T. gondii* infection is believed to result directly from cell lysis by the parasite.²⁴ Inflammatory reactions cause secondary problems, including cystoid macular edema, vitreitis, anterior chamber inflammation, and retinal vasculitis.²⁴ Corticosteroids, which decrease these inflammation-associated problems, are therefore given with antimicrobial agents. Systemic corticosteroids are used by nearly all respondents for treating lesions threatening the macula or optic nerve head. Only rarely did respondents state that they have treated patients with corticosteroids as single therapy. Without concurrent antiparasitic therapy, the suppression of immune defense mechanisms by corticosteroids can lead to fulminant *T. gondii* infection, but when given concurrently with antimicrobial agents, the use of corticosteroids has never been shown to worsen the underlying infection.²⁵ Further controversy exists as to how long, if at all, antimicrobial therapy must be given before initiating corticosteroid therapy. The start of corticosteroid administration is sometimes delayed to allow adequate blood levels of the antimicrobials to be reached.²⁶ Whether this delay is clinically necessary is unknown. Respondents are evenly divided among those beginning corticosteroids concurrently with antimicrobial agents and those waiting 24 to 48 hours.

Topical corticosteroids are used for anterior segment inflammation by nearly all respondents. There is little controversy surrounding their use, probably because *T. gondii* has never been isolated from anterior segment structures except in an immunocompromised patient.²⁷

Experience with periocular corticosteroid injections among respondents is limited. Its use has been discouraged because of experiences in which it has been associated with uncontrollable spread of infection, presumably because of intense suppression of host protective mechanisms.²⁸

Adjunctive therapy for active ocular toxoplasmosis, including laser photocoagulation, cryotherapy, or vitrectomy, has been used by nearly one third of the respondents. A controlled study evaluating the role of these adjunctive therapies in treating active toxoplasmic infections has yet to be conducted. Laser photocoagulation was the most frequently used modality, with the presumed goal of encircling an active lesion with a region of photocoagulated retina, thereby limiting cell-to-cell spread of infection. Laser photocoagulation will not prevent recurrences from distant satellite foci and cannot be administered in the presence of moderate to severe vitreous inflammation. Cryotherapy has been used for peripheral lesions in patients having contraindications to medical therapy. Vitrectomy has been used for severe or persistent vitreous inflammation in patients with active lesions, although this procedure is more commonly used for removal of persistent vitreous opacities in otherwise quiet eyes. Respondents generally reported favorable outcomes for each of these modalities.

Ocular toxoplasmosis in the pregnant woman is an important issue since conventional medical therapy may be teratogenic²⁹ and maternally acquired disease can result in fetal infection. Over one third of respondents have treated patients who were pregnant with active ocular toxoplasmosis. All stated that they will treat the woman to preserve her vision, with most using the same ophthalmic criteria for beginning treatment as in the nonpregnant patient. The teratogenicity of dihydrofolate reductase inhibitors has not been convincingly demonstrated in humans.³⁰ Nevertheless, only three of 20 respondents (15%) who treat pregnant patients with ocular toxoplasmosis use pyrimethamine. The remainder use sulfadiazine (alone or concurrently with either clindamycin or corticosteroids), spiramycin alone, or clindamycin alone. Spiramycin is a macrolide antibiotic with anti-*T. gondii* activity that has minimal side effects and may decrease the incidence of congenitally infected infants.³¹ Spiramycin use among members of the American Uveitis Society is limited, because it is only available in the

United States on a compassionate-use basis. Additionally, six of 18 respondents (33%) stated they have treated acquired disease in the woman to protect the fetus. There is little concern about the fetus in recurrent disease since preexisting maternal antibodies are believed to be protective.

Few American Uveitis Society members (four of 57, 7%) have treated newborns with active ocular toxoplasmosis. They initiate treatment for any active retinal disease with a course of therapy lasting until at least 1 year of age, independent of lesion resolution. Given the systemic nature of active congenital disease, most cases are usually managed by pediatricians.

Systemic dissemination of *T. gondii* is a frequent complication of many immunodeficiency disease processes including those caused by malignancies,³² corticosteroid or cytotoxic therapy,³³ and the acquired immunodeficiency syndrome.³⁴ Ocular toxoplasmosis in patients with AIDS usually responds favorably to antiparasitic therapy.³⁴ Most respondents have treated immunocompromised patients with active ocular toxoplasmosis, with HIV-related illnesses comprising most of the cases seen. Although most (20 of 35, 57%) use the same criteria for beginning treatment as for immunocompetent patients, an increased proportion (11 of 35, 31%) begin treatment in the presence of any active lesion when the patient is immunocompromised. Most administer the same antimicrobial/antiparasitic agents as for immunocompetent patients, although some (four of 35, 11%) withhold pyrimethamine and corticosteroids from therapy. Pyrimethamine use is sometimes avoided because of preexisting bone marrow suppression, and corticosteroid use is avoided to prevent further suppression of host immune mechanisms. Other considerations should be the high incidence of sulfonamide allergies among patients with AIDS and that zidovudine (an antiretroviral agent used commonly in patients with AIDS) has been shown to be antagonistic to pyrimethamine, which may lead to treatment failures if both of these agents are used concurrently.³⁵

Like many infections in immunocompromised patients, toxoplasmosis tends to reactivate if antiparasitic therapy is discontinued.³⁴ Maintenance therapy with lower, suppressive dosages of antimicrobial agents may prevent the reactivation of disease. Most respondents (24 of 38, 63%) administer maintenance antimi-

crobial therapy for the duration of the immunocompromised state with clindamycin being the most frequently used agent followed by sulfadiazine given at reduced dosages. The remainder of respondents administer pyrimethamine, doxycycline, or minocycline as suppressive therapy. Follow-up of these patients is performed more frequently to monitor for reactivation of ocular disease.

This study provides a better understanding of current treatment practices for ocular toxoplasmosis and clearly demonstrates a diversity of opinions among uveitis specialists. This finding probably reflects the lack of evidence demonstrating the superiority of any given therapeutic regimen and suggests the need for prospective investigations. Information obtained from this study could be used in the design of a study comparing different regimens as well as the need to treat different lesions based on their clinical characteristics.

The results of this study are presented as information only and are not intended as treatment recommendations by the authors or by the American Uveitis Society.

References

1. Henderly, D. E., Genstler, A. J., Smith, R. E., and Rao, N. A.: Changing patterns of uveitis. *Am. J. Ophthalmol.* 103:131, 1987.
2. Drugs for parasitic infections. *Med. Lett.* 32:23, 1990.
3. Eyles, D. E., and Coleman, N.: Synergistic effect of sulfadiazine and Daraprim against experimental toxoplasmosis in the mouse. *Antibiot. Chemother.* 3:483, 1953.
4. Acers, T. E.: Toxoplasmic retinochoroiditis. A double blind therapeutic study. *Arch. Ophthalmol.* 71:58, 1964.
5. Perkins, E. S., Smith, C. H., and Schofield, P. B.: Treatment of uveitis with pyrimethamine (Daraprim). *Br. J. Ophthalmol.* 40:577, 1956.
6. Rothova, A., Buitenhuis, H. J., Meenken, C., Baarsma, G. S., Boen-Tan, T. N., de Jong, P. T. V. M., Schweitzer, C., Timmerman, Z., de Vries, J., Zaal, M., and Kijlstra, A.: Therapy in ocular toxoplasmosis. *Int. Ophthalmol.* 13:415, 1989.
7. Ghartey, K. N., and Brockhurst, R. J.: Photocoagulation of active toxoplasmic retinochoroiditis. *Am. J. Ophthalmol.* 89:858, 1980.
8. Spalter, H. F., Campbell, C. J., Noyori, K. S., Rittler, M. C., and Koester, C. J.: Prophylactic photocoagulation of recurrent toxoplasmic retinochoroiditis. *Arch. Ophthalmol.* 75:21, 1966.

9. Dobbie, J. G.: Cryotherapy in the management of *Toxoplasma* retinochoroiditis. *Trans. Am. Acad. Ophthalmol. Otolaryngol.* 72:364, 1968.
10. Fitzgerald, C. R.: Pars plana vitrectomy for vitreous opacity secondary to presumed toxoplasmosis. *Arch. Ophthalmol.* 98:321, 1980.
11. Holland, G. N., Buhles, W. C., Mastre, B., Kaplan, H. J., and the UCLA CMV Retinopathy Study Group: A controlled retrospective study of ganciclovir treatment for cytomegalovirus retinopathy. *Arch. Ophthalmol.* 107:1759, 1989.
12. Nussenblatt, R. B., Palestine, A. G., Chan, C.-C., and Roberge, F.: Standardization of vitreal inflammatory activity in intermediate and posterior uveitis. *Ophthalmology* 92:467, 1985.
13. Eyles, D. E., and Coleman, N.: An evaluation of the curative effects of pyrimethamine and sulfadiazine, alone and in combination, on experimental mouse toxoplasmosis. *Antibiot. Chemother.* 5:529, 1955.
14. Doft, B. H., and Gass, D. M.: Punctate outer retinal toxoplasmosis. *Arch. Ophthalmol.* 103:1332, 1985.
15. Matthews, J. D., and Weiter, J. J.: Outer retinal toxoplasmosis. *Ophthalmology* 95:941, 1988.
16. Nguyen, B. T., Stadtsbaeder, S., and Horvat, F.: Comparative effect of trimethoprim and pyrimethamine, alone and in combination with a sulfonamide, on *Toxoplasma gondii*. In vitro and in vivo studies. In Siegenthaler, W., and Luthy, R. (eds.): *Current Chemotherapy. Proceedings of the Tenth International Congress of Chemotherapy*. Washington, D.C., American Society for Microbiology, 1978, pp. 137-140.
17. Eyles, D. E., and Coleman, N.: The relative activity of the common sulfonamides against experimental toxoplasmosis in the mouse. *Am. J. Trop. Med. Hyg.* 2:54, 1953.
18. ———: The effect of sulfadimetine, sulfisoxazole, and sulfapyrazine against mouse toxoplasmosis. *Antibiot. Chemother.* 5:525, 1955.
19. Tabbara, K. F., and O'Connor, G. R.: Treatment of ocular toxoplasmosis with clindamycin and sulfadiazine. *Ophthalmology* 87:129, 1980.
20. Tabbara, K. F., Sakuragi, S., and O'Connor, G. R.: Minocycline in the chemotherapy of murine toxoplasmosis. *Parasitology* 84:297, 1982.
21. Tabbara, K. F., and O'Connor, G. R.: Ocular tissue absorption of clindamycin phosphate. *Arch. Ophthalmol.* 93:1180, 1975.
22. McMaster, P. R. B., Powers, K. G., Finerty, J. F., and Lunde, M. N.: The effect of two-chlorinated lincomycin analogues against acute toxoplasmosis in mice. *Am. J. Trop. Med. Hyg.* 22:14, 1973.
23. Lakhanpal, V., Schocket, S. S., and Nirankari, V. S.: Clindamycin in the treatment of toxoplasmic retinochoroiditis. *Am. J. Ophthalmol.* 95:605, 1983.
24. O'Connor, G. R.: The influence of hypersensitivity on the pathogenesis of ocular toxoplasmosis. *Trans. Am. Ophthalmol. Soc.* 68:501, 1970.
25. ———: Manifestations and management of ocular toxoplasmosis. *Bull. N.Y. Acad. Med.* 50:192, 1974.
26. Kaufman, H. E., and Caldwell, L. A.: Pharmacological studies of pyrimethamine (Daraprim) in man. *Arch. Ophthalmol.* 61:885, 1959.
27. Rehder, J. R., Burnier, M., Jr., Pavesio, C. E., Kim, M. K., Rigueiro, M., Petrilli, A. M. N., and Bel-fort, R., Jr.: Acute unilateral toxoplasmic iridocyclitis in an AIDS patient. *Am. J. Ophthalmol.* 106:740, 1989.
28. Nozik, R. A., and O'Connor, G. R.: Studies on experimental ocular toxoplasmosis in the rabbit. II. Attempts to stimulate recurrences by local trauma, epinephrine, and corticosteroids. *Arch. Ophthalmol.* 84:788, 1970.
29. Harpey, J. P.: Pyrimethamine in pregnancy. *Lancet* 2:1193, 1983.
30. Pyrimethamine combinations in pregnancy. *Lancet* 2:1005, 1983.
31. Desmonts, G., and Courvreur, J.: Congenital toxoplasmosis. A prospective study of 378 pregnancies. *N. Engl. J. Med.* 290:1110, 1974.
32. Derouin, F., Gluckman, E., Bearvais, B., Devergie, A., Melo, R., Monny, M., and Lariviere, M.: *Toxoplasma* infection after human allogeneic bone marrow transplantation. Clinical and serological study of 80 patients. *Bone Marrow Transplant.* 1:67, 1986.
33. Dubin, H. V., Courter, M. H., and Harrell, E. R.: Toxoplasmosis. A complication of corticosteroid- and cyclophosphamide-treated lupus erythematosus. *Arch. Dermatol.* 104:547, 1971.
34. Holland, G. N., Engstrom, R. E., Jr., Glasgow, B. J., Berger, B. B., Daniels, S. A., Sidikaro, Y., Harmon, J. A., Fischer, D. H., Boyer, D. S., Rao, N. A., Eagle, R. C., Jr., Kreiger, A. E., and Foos, R. Y.: Ocular toxoplasmosis in patients with the acquired immunodeficiency syndrome. *Am. J. Ophthalmol.* 106:653, 1988.
35. Israelski, D. M., Tom, C., and Remington, J. S.: Zidovudine antagonizes the action of pyrimethamine in experimental infection with *Toxoplasma gondii*. *Antimicrob. Agents Chemother.* 33:30, 1989.

Recognition and Removal of the Posterior Cortical Vitreous During Vitreoretinal Surgery for Impending Macular Hole

Calvin E. Mein, M.D., and Harry W. Flynn, Jr., M.D.

Vitreoretinal surgery for impending macular hole includes recognition and removal of the posterior cortical vitreous. Previously described surgical techniques for removal of cortical vitreous used either rigid instruments (a tapered extrusion needle or a barbed microvitreoretinal blade) or a short fenestrated soft-tipped suction needle. We used a technique with the cannulated extrusion needle that detects the presence of the posterior cortical vitreous and facilitates safe removal of this layer from the retina. Although this technique is most useful when performing vitrectomy for impending macular hole, it may also be used during vitrectomy for other conditions with uncertain detachment of the posterior cortical vitreous.

RECENT REPORTS have suggested that pars plana vitrectomy may improve the long-term visual prognosis for patients with stage 1 or 2 idiopathic macular holes.¹⁻³ Stage 1-A shows a central yellow spot (measuring 100 to 200 μm in diameter), which represents a foveolar detachment. Stage 1-B shows an enlargement of the process to form a yellow ring (approximately 200 to 350 μm in diameter), which represents a foveal detachment. In Stage 2, the yellow ring becomes enlarged and a full-thickness retinal dehiscence develops within several weeks or months.¹

Separation and removal of the posterior cortical vitreous have been reported to be important

aspects of successful surgery^{2,3} but are often difficult because the posterior cortical vitreous is clear. Because there are no visual clues to complete posterior vitreous removal, the surgeon may think that a complete vitrectomy has been performed when in reality the posterior cortical vitreous remains attached in the posterior pole. The use of either a tapered extrusion needle,² the fenestrated silicone-tipped suction needle,³ or a barbed microvitreoretinal blade⁴ has been reported as a means of separating the posterior cortical vitreous from the retina in the posterior pole. We used a technique with the cannulated extrusion needle⁵ that detects the clear cortical vitreous and facilitates safe removal of this layer from the retina.

Case Report

A 75-year-old woman had blurred vision and metamorphopsia in the left eye for two months. Visual acuity was R.E.: 20/20 and L.E.: 20/60. Results of examination of the right eye were normal. Slit-lamp biomicroscopy of the left eye disclosed an attached posterior vitreous with a yellow ring lesion in the fovea, representing a stage 1-B macular hole.

After informed consent was obtained from the patient, a pars plana vitrectomy was performed on the left eye. After a central vitrectomy was completed, the cannulated extrusion needle was used to inspect the posterior pole for remaining cortical vitreous. As the cannula approached the retina along the superotemporal vascular arcade with gentle aspiration applied, the soft-tipped cannula deviated in a direction perpendicular to the retina as cortical vitreous became impaled in the tip (Fig. 1). This diagnostic test confirmed the presence of a layer of residual clear, cortical vitreous. While stronger suction was applied (Fig. 2) through the cannula, an illuminated spatula was used as a second instrument to elevate the posterior hyaloid from the retina. Gentle trac-

Accepted for publication Jan. 16, 1991.

From the Brooke Army Medical Center, San Antonio, Texas (Dr. Mein); and Department of Ophthalmology, University of Miami Medical School, Bascom Palmer Eye Institute, Miami, Florida (Dr. Flynn). The opinions or assertions contained herein are the private views of the authors and are not to be construed as reflecting the views of the Department of the Army or the Department of Defense.

Reprint requests to Harry W. Flynn, Jr., M.D., Bascom Palmer Eye Institute, P.O. Box 016880, Miami, FL 33101.

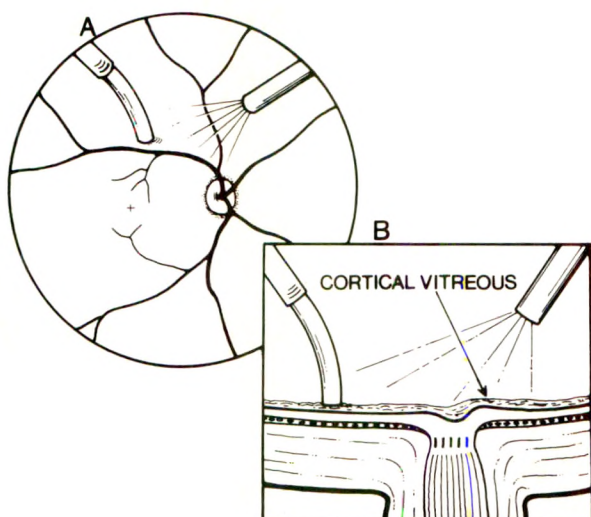


Fig. 1 (Mein and Flynn). A, Posterior segment illustration showing deviation of the flexible cannula with cortical vitreous impaled in the tip of the instrument. B, Cross-sectional view.

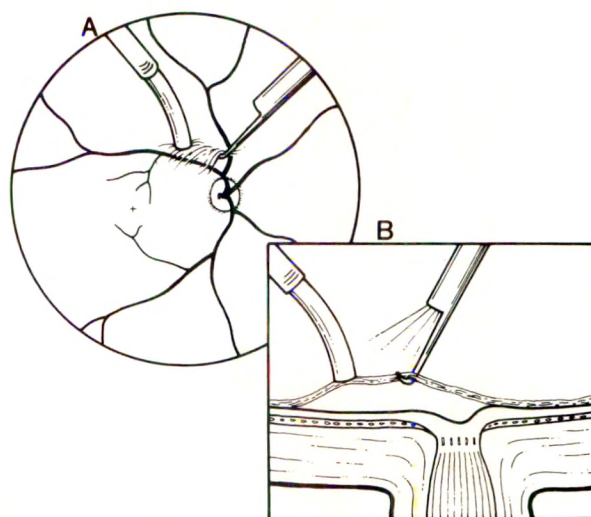


Fig. 2 (Mein and Flynn). A, Posterior segment illustration showing elevation of the cortical vitreous with the cannula and separation of this layer of vitreous with the illuminated spatula. B, Cross-sectional view.

tion was applied until detachment of the posterior cortical vitreous was observed. The vitrectomy instrument was then used to remove the posterior cortical vitreous.

The cannulated extrusion needle was again introduced into the eye. As the needle approached the posterior pole with gentle suction applied, no further deviation of the cannula occurred (Fig. 3), which indicated that all posterior cortical vitreous had been removed successfully.

Postoperatively, visual acuity improved to 20/30 in the left eye. Mild retinal pigment epithelial mottling was observed, but the yellow foveal lesion resolved. Some formed vitreous remained in the anterior periphery, but no vitreous was visible in the posterior pole. Visual acuity remained 20/30 at the six-month follow-up visit.

Discussion

Vitrectomy surgery for impending macular hole may be difficult because of the need to induce posterior cortical vitreous separation. The surgeon may wonder if the clear posterior vitreous was indeed removed. The use of either a nonflexible tapered metal extrusion needle, a fenestrated silicone-tipped needle, or a barbed microvitrectomy blade may not easily or safe-

ly allow recognition of clear residual posterior cortical vitreous.

The flexibility of the cannulated extrusion needle makes it an ideal instrument for both recognition and removal of the residual vitreous. When the vitreous is aspirated into the port of the cannula, the surgeon can see a definite deviation of the cannula, similar to the deviation of a divining rod in search of water. If

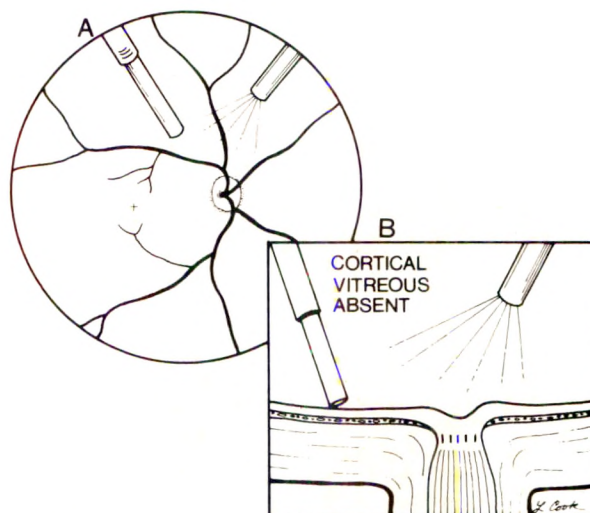


Fig. 3 (Mein and Flynn). A, Posterior segment illustration showing the flexible cannula touching the surface of the retina without deviation of the tip. B, Cross-sectional view.

the posterior cortical vitreous remains, it is impossible to touch the retina with the soft-tipped cannula. Gentle maneuvering of the cannula further confirms the presence of a layer of formed vitreous, because the cannula seems to stick to this vitreous well above the surface of the retina. The use of an illuminated spatula to separate mechanically the cortical vitreous has been previously described by Han, Abrams, and Aaberg,⁴ but the second instrument was either a tapered blunt extrusion needle or microvitreoretinal blade. Once this layer of vitreous has been removed with the vitrectomy instrument, the surgeon can test for residual cortical vitreous. If the soft-tipped cannula does touch the retina directly, the surgeon can be confident that removal of the posterior cortical vitreous was accomplished.

We have found that this technique offers increased safety in testing for complete removal of the posterior cortical vitreous when performing vitrectomy for impending macular hole and

for other conditions with uncertain detachment of the posterior cortical vitreous.

References

1. Gass, J. D. M.: Idiopathic senile macular hole. *Arch. Ophthalmol.* 106:629, 1989.
2. Smiddy, W. E., Michels, R. G., Glaser, B. M., and de Bustros, S.: Vitrectomy for impending idiopathic macular holes. *Am. J. Ophthalmol.* 105:371, 1988.
3. Jost, B. F., Hutton, W. L., Fuller, D. G., Vaiser, A., Snyder, W. B., Fish, G. E., Spencer, R., and Birch, D. G.: Vitrectomy in eyes at risk for macular hole formation. *Ophthalmology* 97:843, 1990.
4. Han, D. P., Abrams, G. W., and Aaberg, T. M.: Surgical excision of attached posterior hyaloid. *Arch. Ophthalmol.* 106:998, 1988.
5. Flynn, H. W., Jr., Davis, J. L., Parel, J. M., and Lee, W. G.: Applications of a cannulated extrusion needle during vitreoretinal microsurgery. *Retina* 8:42, 1988.

OPHTHALMIC MINIATURE

No one who has ever met Gorbachev comes away without mentioning his penetrating eyes. Gorbachev's gaze is commanding—his retinas sometimes a deep brown, sometimes a shining charcoal black. These magnetic eyes radiate power, intensity, energy—abnormal energy. I spoke with him briefly during his visit to Washington in December 1987, and I remember that his eyes were like lasers, locking into mine, never shifting, never blinking.

Hedrick Smith, *The New Russians*
New York, Random House, 1990, p. 37

Ocular Findings in Patients With Autosomal Dominant Retinitis Pigmentosa and Rhodopsin, Proline-347-Leucine

Eliot L. Berson, M.D., Bernard Rosner, Ph.D., Michael A. Sandberg, Ph.D.,
Carol Weigel-DiFranco, M.A., and Thaddeus P. Dryja, M.D.

We studied the ocular findings in eight unrelated patients with a form of autosomal dominant retinitis pigmentosa and the same cytosine-to-thymine transition in the second nucleotide of codon 347 of the rhodopsin gene. This mutation, detected in leukocyte DNA, corresponds to a substitution of leucine for proline in amino acid 347 of the rhodopsin protein, and, therefore, we designated this form of retinitis pigmentosa as rhodopsin, proline-347-leucine. On average, these patients had significantly smaller visual field areas and smaller electroretinogram amplitudes than 140 unrelated patients of comparable age with dominant retinitis pigmentosa without this mutation. The findings in eight relatives with this mutation from three of these families are presented to provide examples of the variability that exists in the clinical severity of this disease.

A RESTRICTION fragment length polymorphism within the long arm of human chromosome 3 has been linked to the disease trait in a large family in Ireland with autosomal dominant retinitis pigmentosa.¹ Since the rhodopsin gene also maps to the long arm of chromosome 3^{2,3} and since rhodopsin is expressed in rod photo-

receptors that are affected early in this disease,^{4,5} we have been searching for abnormalities in the rhodopsin gene in the leukocyte DNA of patients with dominant retinitis pigmentosa.

We previously described four distinct point mutations in the gene coding for rhodopsin.^{6,7} Of 148 unrelated patients from separate families residing in the United States or Canada with autosomal dominant retinitis pigmentosa, 27 carry one of these four mutations. Each mutation corresponds to a single amino acid substitution in the rhodopsin protein. These rhodopsin mutations and their frequencies by family are as follows: proline-23-histidine, 17 cases (12%); proline-347-leucine, eight cases (5%); proline-347-serine, one case (0.5%); and threonine-58-arginine, one case (0.5%). Only one mutation has been found in any given family, and each mutation has segregated perfectly with the disease trait in the families studied. We have not observed these mutations in 106 unrelated normal individuals. These results suggest that these mutations are the cause of some forms of dominant retinitis pigmentosa.^{6,7}

We studied the ocular findings in eight unrelated patients with dominant retinitis pigmentosa and rhodopsin, proline-347-leucine. Their findings are compared with those from 140 patients without this mutation. We also studied eight relatives from three of these families to show the range of abnormalities that exists among patients with this mutation.

Patients and Methods

We reviewed the clinical findings of 148 patients, ages 18 to 49 years, with autosomal dominant retinitis pigmentosa who had donated a blood specimen for molecular genetic studies of their leukocyte DNA. All 148 patients

Accepted for publication Feb. 18, 1991.

From the Berman-Gund Laboratory for the Study of Retinal Degenerations and the Howe Laboratory of Ophthalmology, Harvard Medical School, Massachusetts Eye and Ear Infirmary, Boston, Massachusetts. This study was supported in part by National Eye Institute grants EY00169 and EY02014 and grants from the National Retinitis Pigmentosa Foundation, Baltimore, Maryland, and the George Gund Foundation, Cleveland, Ohio. Dr. Berson is a Research to Prevent Blindness Senior Scientific Investigator.

Reprint requests to Eliot L. Berson, M.D., Massachusetts Eye and Ear Infirmary, 243 Charles St., Boston, MA 02114.

TABLE 1
FINDINGS ON HISTORY IN AFFECTED PATIENTS

CASE NO., FAMILY NO., AGE (YRS), SEX	AGE OF ONSET OF NIGHT BLINDNESS (YRS)	AGE OF ONSET OF DIFFICULTY WITH SIDE VISION (YRS)
1, 6003, 22, M	14	14
2, 3570, 25, M	12	20
3, 0140, 30, M	Near birth	12
4, 6073, 31, F	8	16
5, 5683, 32, F	13	27
6, 5864, 35, F	16	22
7, 0771, 35, M	6	23
8, 6473, 45, M	18	21

were from separate families and resided in the United States or Canada. Each patient was from a family with a dominant mode of transmission of retinitis pigmentosa over at least three consecutive generations. Eight of these patients had a cytosine-to-thymine transition heterozygously in the second nucleotide base of codon 347 (cytosine-cytosine-guanine to cytosine-thymine-guanine) corresponding to a substitution of leucine for proline, whereas 140 of these patients did not have this mutation.⁷ All 148 patients had retinal arteriolar narrowing; most had intraretinal bone spicule pigmentation. We also reviewed the ocular findings in eight clini-

cally affected relatives of three of the eight patients with this mutation. These relatives were selected because they had already provided blood specimens for DNA analysis; all eight relatives also had the same cytosine-to-thymine transition in the second nucleotide base of codon 347 of the rhodopsin gene.

All eight patients with this mutation had European family origin with no single country predominating. Three reside in New England, two in the mid-Atlantic states, and three in midwestern states.

The 148 patients with dominant retinitis pigmentosa completed a questionnaire regarding the age of onset of night blindness and age of onset of difficulty with side or peripheral vision. We evaluated their distance Snellen and Ferris visual acuities, kinetic Goldmann visual fields, intraocular pressure by applanation tonometry, dark-adapted full-field electroretinograms, retinal visual acuities, slit-lamp appearance of each lens, and fundus appearance by ophthalmoscopy as described previously.⁸ Slit-lamp examination was performed to determine presence or absence of a central posterior subcapsular cataract in each eye. Ophthalmoscopic examination was performed to determine whether or not cystoid macular edema could be seen and whether intraretinal bone spicule pigment was in the periphery in all four quadrants.

TABLE 2
FINDINGS ON OCULAR EXAMINATION IN AFFECTED PATIENTS

CASE NO., AGE (YRS)	EYE	VISUAL ACUITY			REFRACTIVE ERROR	LENS	INTRARETINAL BONE SPICULE PIGMENT IN FOUR QUADRANTS
		SNELLEN	FERRIS*	RETINAL			
1, 22	R.E.	20/27	54	20/33	+0.50 -1.25 × 95	Clear	Yes
	L.E.	20/30	47	20/37	+0.50 -1.75 × 80	Clear	Yes
2, 25	R.E.	20/85	24	20/112	+2.00 -1.50 × 172	Posterior subcapsular opacity	Yes
	L.E.	20/82	31	20/120	+3.00 -1.87 × 170	Posterior subcapsular opacity	Yes
3, 30	R.E.	20/20	59	20/20	+0.87 -0.87 × 15	Clear	Yes
	L.E.	20/20	59	20/24	+0.87 -1.12 × 160	Clear	Yes
4, 31	R.E.	20/21	58	20/20	-1.37 -0.62 × 7	Posterior subcapsular opacity	Yes
	L.E.	20/21	58	20/20	-1.75 -1.00 × 180	Posterior subcapsular opacity	Yes
5, 32	R.E.	20/33	50	20/36	+0.87 -2.50 × 15	Posterior subcapsular opacity	Yes
	L.E.	20/52	39	20/42	+0.50 -3.00 × 177	Posterior subcapsular opacity	Yes
6, 35	R.E.	20/37	44	20/37	-0.62 -0.50 × 22	Posterior subcapsular opacity	Yes
	L.E.	20/41	41	20/34	+0.37	Posterior subcapsular opacity	Yes
7, 35	R.E.	20/37	44	20/25	-3.25 -0.62 × 60	Posterior subcapsular opacity	Yes
	L.E.	20/30	47	20/25	-3.37 -0.50 × 150	Posterior subcapsular opacity	Yes
8, 45	R.E.	20/93	31	20/102	+1.25 -0.75 × 157	Posterior subcapsular opacity	Yes
	L.E.	20/42	42	20/47	+0.75 -1.25 × 177	Posterior subcapsular opacity	Yes

*Number of letters read; 65 letters equals Snellen equivalent of 20/20.

Visual fields were plotted with a digitizing tablet, and the total area for each eye was quantified by a computer in square degrees and expressed as an equivalent circular area or equivalent circular diameter. Electroretinograms were quantified with respect to peak-to-peak amplitudes for the mixed cone-rod responses to 0.5-Hz white flashes, the cone-isolated responses to 30-Hz white flashes, and the 30-Hz cone b-wave implicit times (that is, the time intervals between each flash of light and the corresponding cornea-positive peak) as described previously.⁹

The data derived from ocular examinations of the 148 patients with dominant retinitis pigmentosa were coded by one person and checked by another; data were then keypunched, verified, and stored on a magnetic tape for data processing. Data were then validated for errors and inconsistencies and corrected as necessary. Comparisons were made between the group of eight unrelated patients with this mutation and the group of 140 unrelated patients without this mutation. Each of the 148 patients was examined twice within six weeks, and an average score for each eye was computed for each test parameter. For the purpose of statistical analysis, an average of these scores for the two eyes was used. Since the distributions of Snellen distance visual acuities, retinal visual acuities, visual field equivalent circular areas, and electroretinogram amplitudes were skewed, the data were transformed using the log_e scale to approximate better a normal distribution for each parameter for purposes of statistical analysis. Data for continuous variables, such as best-corrected visual acuity or spheric refractive error, were analyzed using *t*-tests for univariate analyses.¹⁰ Discrete variables, such as presence or absence of posterior subcapsular cataract in both eyes or presence or absence of bone spicule pigment in all four quadrants of the fundus periphery in both eyes, were analyzed with the Yates corrected chi-square test or Fisher's exact test.¹⁰ Age of onset of night blindness and age of onset of difficulty with side vision were evaluated by using the log-rank life-table method of analysis; patients who did not yet have night blindness or who had not yet reported visual field loss were treated as censored observations with the length of the follow-up period equal to their current age.¹¹ Multiple regression analysis used group membership, age, and sex as the independent variables and selected ocular findings as the dependent variables. This allowed assessment of

TABLE 3
VISUAL FIELDS AND ELECTRORETINOGRAMS IN AFFECTED PATIENTS

CASE NO., AGE (YRS)	EYE	VISUAL FIELD*		ELECTRORETINOGRAM†		
		AREA	DIAMETER	0.5-HZ AMPLI- TUDE (μV)	30-HZ AMPLI- TUDE (μV)	30-HZ IMPLICIT TIME (MSEC)
1, 22	R.E.	7194	96	3.3	1.1	47
	L.E.	6742	93	2.9	1.4	48
2, 25	R.E.	384	22	1.2	1.0	42
	L.E.	326	20	1.7	1.1	43
3, 30	R.E.	2197	53	1.8	1.0	40
	L.E.	2222	53	3.0	1.2	41
4, 31	R.E.	2718	59	3.2	0.7	39
	L.E.	3052	62	2.7	0.6	41
5, 32	R.E.	2075	51	1.6	0.2	34
	L.E.	1992	50	1.6	0.2	34
6, 35	R.E.	186	15	1.1	0.2	43
	L.E.	189	15	NA‡	0.2	47
7, 35	R.E.	1658	46	1.0	0.7	35
	L.E.	1773	47	1.3	0.6	34
8, 45	R.E.	484	25	1.0	0.3	33
	L.E.	536	26	1.0	0.3	34

*Area is the visual field area including peripheral islands in degrees squared to a V_{4e} white test light. Lower limit of normal is 11,399 degrees squared. Diameter is equivalent circular diameter in degrees: $2\sqrt{\frac{\text{area}}{\pi}}$.

†Full-field electroretinograms: normal limits are 0.5-Hz white ≥ 350 μV; 30-Hz white flicker ≥ 50 μV; and 30-Hz b-wave implicit time ≤ 32 msec.

‡NA indicates not available.

differences between the two groups for selected ocular findings after correcting for age and sex.¹⁰

We examined eight affected relatives from three of the families once. Their clinical findings provide additional data on the range of ocular abnormalities seen in patients with this mutation and show examples of some variability of clinical expression of this condition among patients of comparable age.

Results

The eight patients from separate families with dominant retinitis pigmentosa and rhodopsin, proline-347-leucine reported some variability in the age of onset of night blindness (Tables 1 through 3). For example, one patient

TABLE 4
GROUP COMPARISONS OF PATIENTS WITH (GROUP 1) AND WITHOUT (GROUP 2) PROLINE-347-LEUCINE RHODOPSIN MUTATION

PARAMETERS	GROUP 1 (N = 8)	GROUP 2 (N = 140)*	t-STAT	P VALUE	P VALUE (CORRECTED)†
Snellen‡ visual acuity	+0.61 ± 0.49 (20/37)	+0.54 ± 0.54 (20/34)	+0.33	NS	NS
Ferris visual acuity	+45.28 ± 10.48	+48.36 ± 9.16	-0.92	NS	NS
Retinal‡ visual acuity	+0.64 ± 0.59 (20/38)	+0.48 ± 0.40 (20/32)	+1.08	NS	NS
Spheric refractive error	+0.07 ± 1.78	-0.21 ± 3.64	+0.21	NS	NS
Cylindric refractive error	-1.19 ± 0.78	-1.16 ± 0.98	+0.10	NS	NS
Intraocular pressure (mm Hg)	12.16 ± 1.42	11.92 ± 2.08	+0.31	NS	NS
Visual field area (deg²)‡	7.11 ± 1.21 (1224)	7.99 ± 1.32 (2951)	-1.84	NS	.046
0.5-Hz electroretinogram (μV)‡	0.52 ± 0.44 (1.68)	1.79 ± 1.31 (5.99)	-6.57	<.001	.008
30-Hz electroretinogram (μV)‡	-0.62 ± 0.75 (0.54)	+0.65 ± 1.59 (1.91)	-4.27	<.001	.026
30-Hz electroretinogram (msec)	39.44 ± 5.13	42.22 ± 4.37	-1.73	NS	NS

*Ferris visual acuity was measured in 139 patients, retinal visual acuity in 138, and 0.5-Hz electroretinogram in 137.

†P value corrected for age and sex based on multiple regression analysis. NS indicates not significant.

‡Mean value ± standard deviation for this parameter is presented in the natural log_e scale. Geometric mean for visual acuity, shown in parentheses, was calculated as the antilog of the natural log mean × 20. Geometric mean for visual field and electroretinogram amplitude, shown in parentheses, was calculated as the antilog of the natural log mean. Electroretinogram responses to 0.5 Hz that were nondetectable (ie, <1.0 μV) were set to 1.0 μV for purposes of analysis.

reported that the onset of night blindness was near birth, whereas another patient first observed night blindness at age 18 years. Most did not report difficulty with side vision until after age 19 years, but one patient reported onset at age 12 years, whereas another patient denied any loss of side vision until age 27 years. Some interfamilial clinical variability was also evident in the findings on ocular examination.

Some older patients with this mutation reported better distance and retinal visual acuities than younger patients (Table 2). Some older patients retained larger visual field areas than younger patients (Table 3). One patient (Case 6) at age 35 years had a smaller visual field area than another patient (Case 7) at age 35 years.

Mean values for Snellen visual acuity, Ferris visual acuity, retinal visual acuity, spheric and

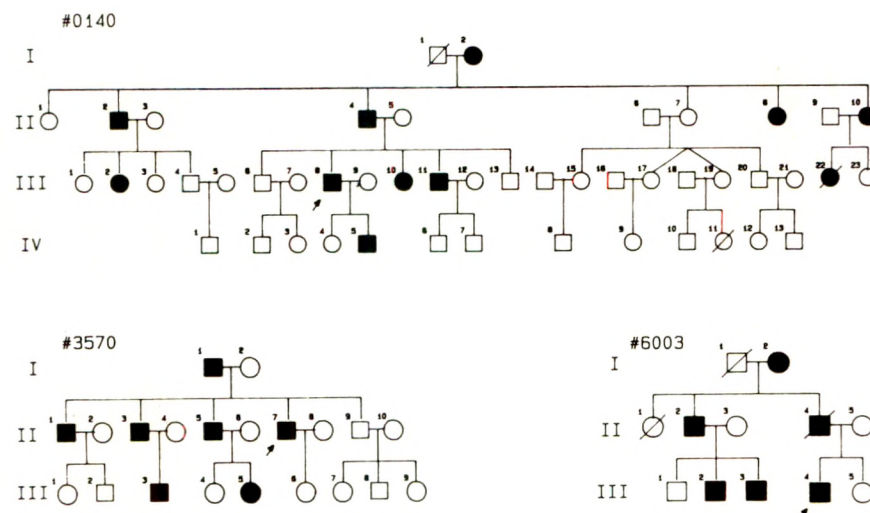


Fig. 1 (Berson and associates). Pedigrees of families 0140, 3570, and 6003 with autosomal dominant retinitis pigmentosa with a cytosine-to-thymine transition in codon 347 of the rhodopsin gene. Solid symbols indicate affected individuals; open symbols indicate unaffected; slashed symbols indicate deceased; oblique arrows indicate Cases 3, 2, and 1, respectively.

TABLE 5
FINDINGS ON HISTORY IN AFFECTED RELATIVES

CASE NO., FAMILY NO., PEDIGREE,* AGE (YRS), SEX	AGE OF ONSET OF NIGHT BLINDNESS (YRS)	AGE OF ONSET OF DIFFICULTY WITH SIDE VISION (YRS)
9, 0140, IV-5, 13, M	2	8
10, 0140, III-10, 16, F	12	12
11, 0140, III-2, 25, F	10	10
12, 0140, III-11, 26, M	10	22
13, 0140, II-8, 42, F	Near birth	Near birth
14, 0140, II-4, 48, M	12	12
15, 3570, II-3, 31, M	Near birth	18
16, 6003, III-2, 18, M	None	13

*Designates relative position in pedigree for each family in Figure 3.

cylindric refractive errors, intraocular pressure by applanation tonometry, visual field area, and electroretinogram amplitudes and cone implicit time for the eight patients with this mutation (Group 1) were compared with the 140 patients without this mutation (Group 2) (Table 4). The mean age (\pm standard deviation) of Group 1 was 31.9 ± 7.0 years and of Group 2 was 32.7 ± 8.3 years (not significant). Sex ratios for Group 1 (five men, three women) and Group 2 (73 men, 67 women) were also not significantly different. Mean spheric and cylindric refractive errors and mean intraocular pressure were

not significantly different between the two groups. Mean visual field area was significantly smaller in Group 1 compared to Group 2 after correcting for age and sex. Mean electroretinogram amplitudes, both to 0.5-Hz white light and to 30-Hz white flicker, were also significantly smaller in Group 1 than in Group 2, whereas mean cone b-wave implicit time to 30-Hz white flicker was not significantly different between the two groups.

A life-table analysis comparing the two groups with respect to age of onset of night blindness by history showed that the median age of onset of night blindness was 12.5 years for Group 1 and 14 years for Group 2 (not significant by log-rank test). A life-table analysis disclosed no difference between the two groups with respect to age of onset of difficulty with side vision by history; the median age of onset of difficulty with side vision was 20.5 years for Group 1 and 23 years for Group 2.

Slit-lamp examination disclosed that six of eight patients (75%) in Group 1 had a central posterior subcapsular cataract in both eyes, whereas 86 of 140 patients (61%) in Group 2 had this finding. Intraretinal bone spicule pigment was noted in all four quadrants of both eyes in all patients in Group 1 and 111 of 140 patients (79%) in Group 2. Cystoid macular edema was seen in both eyes in one of eight patients (12%) in Group 1 and 15 of 140 patients (11%) in Group 2. Comparisons between

TABLE 6
FINDINGS ON OCULAR EXAMINATION IN AFFECTED RELATIVES

CASE NO., FAMILY NO., AGE (YRS)	EYE	SNELLEN VISUAL ACUITY	REFRACTIVE ERROR	LENS	INTRARETINAL BONE SPICULE PIGMENT IN FOUR QUADRANTS
9, 0140, 13	R.E.	20/25	+3.00 -3.25 \times 175	Clear	No
	L.E.	20/20	+3.25 -3.75 \times 180	Clear	No
10, 0140, 16	R.E.	20/25	Plano -2.00 \times 158	Posterior subcapsular cataract	Yes
	L.E.	20/25	Plano -1.75 \times 34	Posterior subcapsular cataract	Yes
11, 0140, 25	R.E.	20/200	+1.25	Clear	Yes
	L.E.	20/200	+1.25	Clear	Yes
12, 0140, 26	R.E.	20/70	+0.50 -1.00 \times 20	Clear	Yes
	L.E.	20/20	+0.50 -0.50 \times 135	Clear	Yes
13, 0140, 42	R.E.	20/400	+1.50 -3.50 \times 180	Posterior subcapsular cataract	Yes
	L.E.	20/400	+1.50 -3.50 \times 180	Posterior subcapsular cataract	Yes
14, 0140, 48	R.E.	20/60	-0.75 -0.75 \times 45	Posterior subcapsular cataract	Yes
	L.E.	20/40	+1.50 -0.75 \times 135	Posterior subcapsular cataract	Yes
15, 3570, 31	R.E.	20/30	+5.00 -2.00 \times 180	Pseudophakia	Yes
	L.E.	20/40	+1.00 -1.50 \times 175	Pseudophakia	Yes
16, 6003, 18	R.E.	20/27	+1.12 -1.75 \times 180	Clear	Yes
	L.E.	20/44	+0.75 -1.62 \times 180	Clear	Yes

TABLE 7
DARK ADAPTATION, VISUAL FIELDS, AND ELECTRORETINOGRAMS IN AFFECTED RELATIVES

CASE NO., FAMILY NO., AGE (YRS)	EYE	DARK ADAPTATION*	VISUAL FIELD†		ELECTRORETINOGRAMS‡		
			AREA	DIAMETER	0.5-HZ AMPLITUDE (μ V)	30-HZ AMPLITUDE (μ V)	30-HZ IMPLICIT TIME (MSEC)
9, 0140, 13	R.E.	2.5	8231	102	41	47	41
	L.E.	2.5	7274	96	41	35	41
10, 0140, 16	R.E.	1.5	9847	112	53	24	34
	L.E.	1.5	10070	113	NA§	NA	NA
11, 0140, 25	R.E.	4.0	3138	63	ND§	ND	ND
	L.E.	NA	3830	70	ND	ND	ND
12, 0140, 26	R.E.	2.5	1246	40	1.0	0.2	39
	L.E.	2.3	1118	38	1.4	0.4	39
13, 0140, 42	R.E.	4.0	NA	NA	ND	ND	ND
	L.E.	NA	NA	NA	NA	NA	NA
14, 0140, 48	R.E.	3.5	78	10	ND	ND	ND
	L.E.	3.5	78	10	NA	NA	NA
15, 3570, 31	R.E.	3.0	305	20	<1.0	0.3	34
	L.E.	3.0	613	28	<1.0	0.3	34
16, 6003, 18	R.E.	NA	10861	118	7.7	6.1	45
	L.E.	NA	11821	123	8.1	5.5	45

*Final threshold after 45 minutes of dark adaptation expressed as log units above normal to 11-degree white test light in Goldmann-Weekers adaptometer fixated centrally or 7 degrees above fovea.

†Area is the visual field including peripheral islands in degrees squared to a V_{40} white test light. Lower limit of normal is 11,399 degrees squared. Diameter is equivalent circular diameter in degrees: $2\sqrt{\frac{\text{area}}{\pi}}$.

‡Full-field electroretinograms: normal limits are 0.5-Hz white $\geq 350 \mu$ V; 30-Hz white flicker $\geq 50 \mu$ V; and 30-Hz b-wave implicit time ≤ 32 msec.

§NA indicates not available and ND indicates not detectable without computer averaging (ie, $< 10 \mu$ V).

Group 1 and Group 2 for these three parameters disclosed no statistically significant differences.

In eight affected relatives from three families (Fig. 1), ages at onset of night blindness and visual field loss by history differed among members of the same family (Tables 5 through 7). For example, in family 3570 one member reported night blindness near birth, whereas his brother (Case 2 in Table 1) reported night blindness at age 12 years. In family 0140, Case 12 noticed loss of side vision at age 22 years, whereas his father (Case 14) noticed loss of side vision at age 12 years. In family 0140 (Table 6), visual acuities ranged from 20/200 in Case 11, age 25 years, to 20/20 in Case 3, age 30 years (Table 2). Case 11 had a 4.0-log unit increase of dark adaptation threshold at age 25 years, whereas Case 12 had a 2.3- to 2.5-log unit increase at age 26 years.

Clinically affected patients from family 0140 younger than age 20 years with rhodopsin, proline-347-leucine showed nondetectable rod responses to blue light, reduced responses to single flashes of white light, and reduced and

delayed cone responses to 30-Hz white flicker (Fig. 2). One patient (Case 11), age 25 years, had nondetectable responses to all test stimuli. This patient was representative, since all patients with this mutation older than age 20 years whom we examined had electroretinogram responses that were less than 10μ V to 0.5-Hz white light or 30-Hz white flicker.

In fundus photographs from four patients from separate families, Case 12 (photographed at age 26 years) from one family showed more intraretinal pigment than Case 4 (photographed at age 32 years) from another family (Fig. 3). The fundus photographs of Case 6 at age 38 years and Case 8 at age 47 years showed typical deposition of intraretinal pigment around the midperiphery.

Discussion

Eight unrelated patients with autosomal dominant retinitis pigmentosa and rhodopsin,

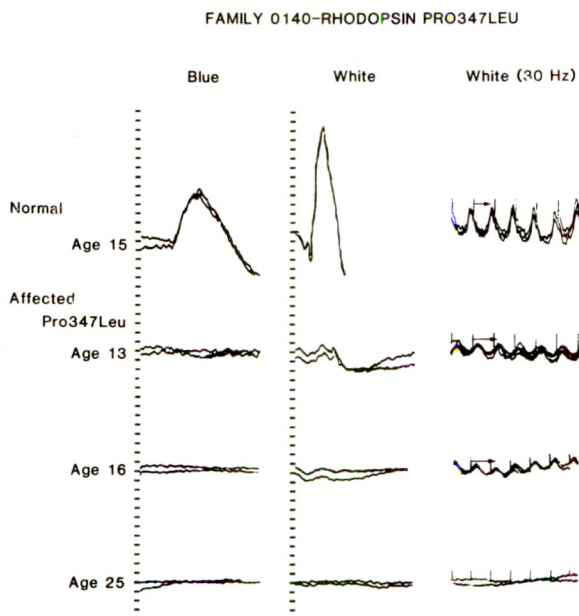


Fig. 2 (Berson and associates). Full-field electroretinograms from an unaffected relative and three affected relatives in family 0140 with autosomal dominant retinitis pigmentosa and rhodopsin, proline-347-leucine. Stimulus onset is the vertical hatched lines for the left and middle columns and vertical lines for the right column. Two or three consecutive sweeps are superimposed. Horizontal arrows in the right column designate cone b-wave implicit times. Calibration symbol (lower right) designates 50 msec horizontally and 100 μ V vertically.

proline-347-leucine had significantly less visual function as monitored by visual field and electroretinogram amplitudes than 140 unrelated patients of comparable average age with autosomal dominant retinitis pigmentosa without this mutation. These data, based on findings at initial visits, suggested two possible explanations for the apparent disparity between these two groups regarding loss of function. The first is that the time of onset of degeneration is earlier in the group with this mutation than in the group without this mutation and that both groups have a similar rate of degeneration. The second possibility is that the rate of degeneration is faster in the group with this mutation than in the group without this mutation. A prospective longitudinal study of subsets of patients with or without this mutation would help to explain this disparity.

The electroretinogram findings differed from those previously described in a group of 17 patients (mean age, 37 years) with autosomal dominant retinitis pigmentosa and rhodopsin,

proline-23-histidine.⁸ Patients with proline-23-histidine had on average larger electroretinogram amplitudes than a group of patients with dominant retinitis pigmentosa without this mutation. The mean electroretinogram response to single 0.5-Hz flashes of white light was almost tenfold larger (that is, 14.4 μ V) than that recorded from patients with proline-347-leucine (that is, 1.7 μ V). The mean cone response to 30-Hz flicker was also tenfold larger for the proline-23-histidine group (that is, 5.5 μ V) compared with that for the proline-347-leucine group (that is, 0.5 μ V). The electroretinogram findings would support the idea that patients with proline-23-histidine generally have a less severe disease than those with rhodopsin, proline-347-leucine.

Patients with the common forms of retinitis pigmentosa lose 16% of remaining full-field electroretinogram amplitude per year to 0.5-Hz white stimuli.⁹ If we assume this same exponential rate of decline applies to patients with either the proline-23-histidine or the proline-347-leucine mutation and that both have the same age of onset, then the proline-23-histidine group, with a mean age of 37 years and an electroretinogram amplitude of 14.4 μ V on initial examination, has an estimated 33 years of remaining vision and would be expected to become virtually blind (that is, ≤ 0.05 μ V) by age 70 years. By the same calculation, the proline-347-leucine group, with a mean age of 32 years and an electroretinogram amplitude of 1.7 μ V on their initial examination, has an estimated 21 years of remaining vision and would be expected to become blind by age 53 years. Although these estimates are based on small numbers and need to be confirmed by a prospective longitudinal study, the available data suggest that patients with rhodopsin, proline-23-histidine would be expected to retain vision 17 years longer than patients with rhodopsin, proline-347-leucine.

Since no clinically unaffected individuals have shown the proline-347-leucine mutation, this form of dominant retinitis pigmentosa can now be diagnosed through analysis of leukocyte DNA. Patients so identified should have an ocular examination and electroretinogram to determine the extent of retinal malfunction, as some variability in clinical expression can exist at a given age among patients with the same mutation. As larger numbers of patients with the proline-347-leucine mutation are identified, this variability can be assessed statistically after taking age into account. Risk factor analy-

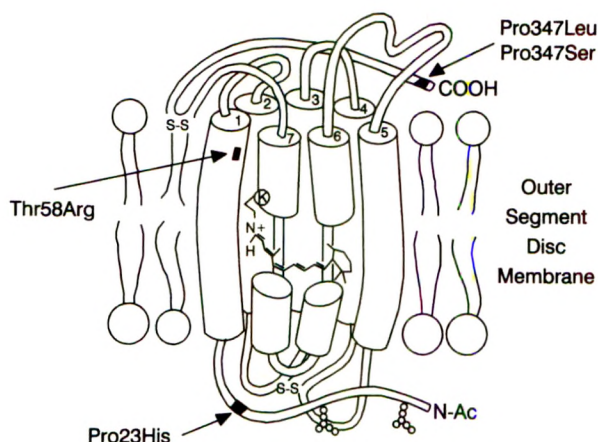


Fig. 5 (Berson and associates). Schematic representation of normal folded rhodopsin molecule in rod outer segment membrane that normally forms a pocket (partially cut away) to hold a molecule of 11-cis-retinal. Positions are shown for four amino acids affected by mutations found in patients with autosomal dominant retinitis pigmentosa. Pro347Leu indicates proline-347-leucine; Pro347Ser indicates proline-347-serine; Thr58Arg indicates threonine-58-arginine; Pro23His indicates proline-23-histidine; N-Ac indicates the acetylated amino terminus of the polypeptide chain; and COOH indicates the carboxy terminus of the molecule.

ses of patients with this mutation followed up over years may help to determine ameliorating or aggravating factors that may be affecting the course of this condition and its expression at a given age, with possible implications for therapy.

Since all the patients we have described with any of the rhodopsin mutations are heterozygotes,⁶⁻⁸ we can speculate that their rod photoreceptors produce normal and mutant molecules of rhodopsin in approximately a 50:50 ratio. The normal molecules presumably are incorporated in the outer segment and account for the presence of some rod function seen in the early stages of this condition. The mutant molecules of rhodopsin are perhaps abnormally degraded in the inner segment; or if they reach the outer segment, these mutant molecules possibly interfere with outer segment function or photoreceptor-pigment epithelial cell interactions.

Each rhodopsin molecule normally traverses the rod outer segment membrane seven times (Fig. 4) and is folded in three dimensions, with the first and seventh transmembrane segments probably in close proximity (Fig. 5). Loops on the intradiscal side as well as the region near the amino-terminal tail are thought to be essen-

tial for the correct folding of the molecule,^{12,13} whereas some loops on the cytoplasmic side appear to interact with transducin as an early step in the phototransduction cascade.¹⁴ The folded molecule normally forms a pocket for vitamin A aldehyde (that is, 11-cis-retinal), which is bound covalently to a lysine residue at position 296, designated by the letter K in the seventh transmembrane segment. The proline-23-histidine mutation may interfere with the overall folding of rhodopsin and thereby modify the capacity of the pocket to hold vitamin A. Since threonine is neutral and arginine is charged, the threonine-58-arginine mutation in the first transmembrane segment may alter the properties of the pocket. It has been speculated that the proline-347-leucine or proline-347-serine mutations may affect assembly or transport of molecules through the inner segment, with consequent accumulation of these molecules in the rough endoplasmic reticulum or in the Golgi apparatus¹⁵; this accumulation may compromise viability of rod photoreceptors. Studies of transgenic mice as well as cultured cell systems with these mutations should help to define the precise mechanisms by which these gene abnormalities lead to rod photoreceptor cell death.

References

1. McWilliam, P., Farrar, G. J., Kenna, P., Bradley, D. G., Humphries, M. M., Sharp, E. M., McConnell, D. J., Lawler, M., Sheils, D., Ryan, C., Stevens, K. J., Daiger, S. P., and Humphries, P.: Autosomal dominant retinitis pigmentosa (ADRP). Localization of an ADRP gene to the long arm of chromosome 3. *Genomics* 5:619, 1989.
2. Sparkes, R. S., Mohandas, T., Newman, S. L., Heinzmann, C., Kaufman, D., Zollman, S., Leveille, P. J., Tobin, A. J., and McGinnis, J. F.: Assignment of the rhodopsin gene to human chromosome 3. *Invest. Ophthalmol. Vis. Sci.* 27:1170, 1986.
3. Nathans, J., Piantanida, R. L., Eddy, R. L., Shows, T. B., and Hogness, D. S.: Molecular genetics of inherited variation in human color vision. *Science* 232:203, 1986.
4. Mandelbaum, J.: Dark adaptation. Some physiologic and clinical considerations. *Arch. Ophthalmol.* 26:203, 1941.
5. Sloan, L. L.: Light sense in pigmentary degeneration of the retina. *Arch. Ophthalmol.* 2:253, 1956.
6. Dryja, T. P., McGee, T., Reichel, E., Hahn, L. B., Cowley, G. S., Yandell, D. W., Sandberg, M. A., and Berson, E. L.: A point mutation of the rhodopsin gene in one form of retinitis pigmentosa. *Nature* 343:364, 1990.

7. Dryja, T. P., McGee, T., Hahn, L. B., Cowley, G. S., Olsson, J. E., Reichel, E., Sandberg, M. A., and Berson, E. L.: Mutations within the rhodopsin gene in patients with autosomal dominant retinitis pigmentosa. *N. Engl. J. Med.* 323:1302, 1990.
8. Berson, E. L., Rosner, B., Sandberg, M. A., and Dryja, T. P.: Ocular findings in patients with dominant retinitis pigmentosa and a rhodopsin gene defect (Pro-23-His). *Arch. Ophthalmol.* 109:92, 1991.
9. Berson, E. L., Sandberg, M. A., Rosner, B., Birch, D. G., and Hanson, A. H.: Natural course of retinitis pigmentosa over a three-year interval. *Am. J. Ophthalmol.* 99:240, 1985.
10. Rosner, B.: *Fundamentals of Biostatistics*, ed. 6. Boston, Duxbury Press, 1989.
11. Peto, R., Pike, M. C., Armitage, P., Breslow, N. E., Cox, D. R., Howard, S. V., Mantel, N., McPherson, K., Peto, J., and Smith, P. G.: Design and analysis of randomized clinical trials requiring prolonged observation of each patient. *Br. J. Cancer* 35:1, 1977.
12. Karnik, S. S., Sakmar, T. P., Chen, H. B., and Khorana, H. G.: Cysteine residues 110 and 187 are essential for the formation of correct structure in bovine rhodopsin. *Proc. Natl. Acad. Sci. USA* 85:8459, 1988.
13. Doi, T., Molday, R. S., and Khorana, H. G.: Role of the intradiscal domain in rhodopsin assembly and function. *Proc. Natl. Acad. Sci. USA* 87:4991, 1990.
14. Franke, R. R., König, B., Sakmar, T. P., Khorana, H. G., and Hofmann, K. P.: Rhodopsin mutants that bind but fail to activate transducin. *Science* 250:123, 1990.
15. Hargrave, P. A., and O'Brien, P. J.: Speculations on the molecular basis of retinal degeneration in retinitis pigmentosa. In Anderson, R. E., Hollyfield, J. G., and LaVail, M. M. (eds.): *Retinal Degenerations*. Boca Raton, Florida, CRC Press, Inc., 1991. In press.

An Eyelash Nidus for Dacryoliths of the Lacrimal Excretory and Secretory Systems

Keith H. Baratz, M.D., George B. Bartley, M.D., R. Jean Campbell, M.D.,
and James A. Garrity, M.D.

We treated two patients with dacryolithiasis secondary to an eyelash. The first patient underwent dacryocystorhinostomy for a stone within the lacrimal sac. In the second patient the dacryolith was removed from a lacrimal gland ductule. Eyelashes found in the tear film or conjunctival fornices during routine examination should be removed to prevent the possible occurrence of dacryolithiasis.

DACRYOLITHS may occur in the lacrimal gland ductules, canaliculi, lacrimal sac, or nasolacrimal duct. Except for canalicular concretions classically associated with *Actinomyces* species infection, the origin of such stones is not well understood. Early case reports of nasolacrimal duct dacryoliths described casts of material containing numerous fungal elements (*Candida albicans*).^{1,2} Subsequent studies of larger numbers of cases varied greatly in finding a correlation between fungal infections and nasolacrimal duct stones.³⁻⁷ Likewise, little is known about the pathogenesis of stone formation in the unusual entity of lacrimal gland ductule stones.⁸

In rare instances, an eyelash may be the nidus for symptomatic dacryolith formation. We treated two patients who had an eyelash-associated dacryolith; in one patient the stone was within the lacrimal sac, and in the other patient the dacryolith formed within a lacrimal gland ductule.

Case Reports

Case 1

A 64-year-old woman had epiphora from the left eye of two weeks' duration. Her history was noncontributory for midfacial trauma, sinus disease, or sinus or nasal surgery. The left eye was quiet and white, and the left lacrimal sac was not palpable. Irrigation of saline through the left inferior canaliculus resulted in near total reflux without mucus or pus through the left superior punctum, although a small amount of irrigant passed into the nose. Because of the acute onset, lack of infection, and partial obstruction, a dacryolith was suspected and treated by dacryocystorhinostomy. The postoperative course was unremarkable. The dacryolith was composed of acellular, amorphous debris surrounded by an eyelash nidus (Figs. 1 and 2).

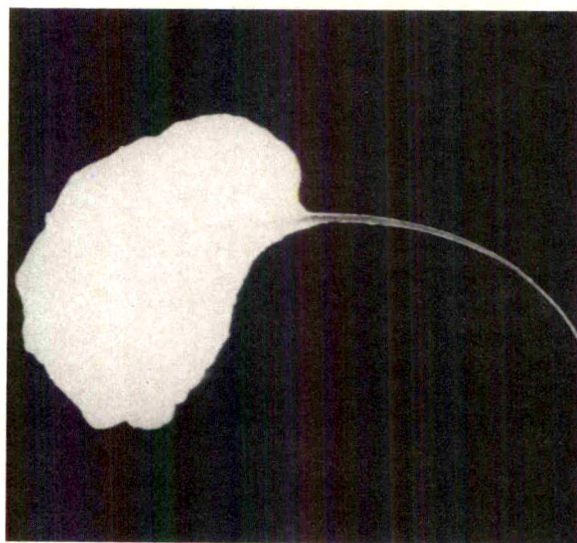


Fig. 1 (Baratz and associates). Case 1. Dacryolith with eyelash nidus removed from the lacrimal sac ($\times 3.5$).

Accepted for publication Feb. 21, 1991.

From the Department of Ophthalmology (Drs. Baratz, Bartley, Campbell, and Garrity) and Section of Surgical Pathology (Dr. Campbell), Mayo Clinic and Mayo Foundation, Rochester, Minnesota. This study was supported in part by an unrestricted grant from Research to Prevent Blindness, Inc.

Reprint requests to George B. Bartley, M.D., Mayo Clinic, 200 First St. S.W., Rochester, MN 55905.

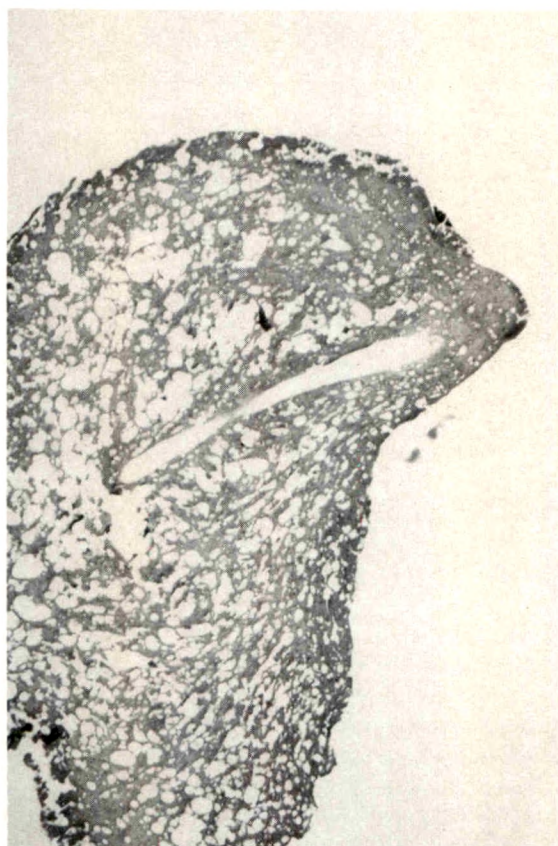


Fig. 2 (Baratz and associates). Case 1. The stone was composed of acellular, amorphous debris surrounding the pseudofollicle from which the eyelash emerged (hematoxylin and eosin, $\times 8$).

Case 2

A 37-year-old man had a one-week history of pain and swelling of his right superotemporal orbit and injection of and discharge from the right eye. He had been aware of a nontender nodule in the region of the right lacrimal gland for approximately five years. Recently, the mass had shifted in position from above to below the lateral canthal tendon.

On examination, the temporal bulbar conjunctiva of the right eye was injected moderately and purulent discharge was noted at the lateral canthus. The temporal aspect of the right upper eyelid was edematous with tenderness on palpation of a 5-mm, firm, mobile, subcutaneous mass immediately inferior to the lateral canthal tendon. With topical anesthesia, the palpebral conjunctiva adjacent to the nodule was incised. A large dacryolith was noted, although it could not be removed from this approach. A lateral canthotomy was done to facili-

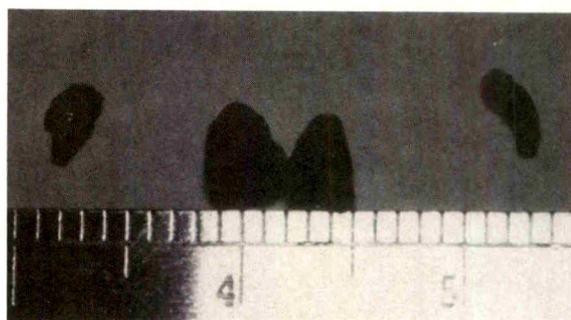


Fig. 3 (Baratz and associates). Case 2. Dacryolith with eyelash nidus removed in several fragments from the lacrimal gland ductule.

tate exposure, and the stone was removed in several fragments (Fig. 3). A densely calcified calculus surrounding an eyelash nidus was apparent on routine histopathologic examination (Fig. 4). A culture for fungus was negative.

Discussion

Dacryoliths are a significant cause of nasolacrimal obstruction requiring dacryocystorhinostomy. In several previously reported series,³⁻⁷ females are affected three times as frequently as males, and dacryolithiasis is more likely to occur in patients younger than 50 years of age (Table). In the series reported by Jones³ of 25 stones in 180 dacryocystorhinostomies, only three dacryoliths were found in 123 patients



Fig. 4 (Baratz and associates). Case 2. The stone was composed of calcium and amorphous material around the eyelash nidus (arrow), which enhanced with polarization (hematoxylin and eosin, $\times 160$).

TABLE
CLINICAL DATA ON PATIENTS WHO UNDERWENT DACRYOCYSTORHINOSTOMY FOR DACRYOLITHIASIS

STUDY	NO. OF DACRYOLITHS: NO. OF DACRYOCYSTO- RHINOSTOMIES	NO. OF DACRYOLITHS IN:	
		MALE: FEMALE	YOUNGER THAN 50 YEARS: OLDER THAN 50 YEARS
Jones ³	25:180	7:15*	22:3
Herzig and Hurwitz ⁴	14:246	NR†	NR†
Berlin, Rath, and Rich ⁵	11:70	1:10	7:4
Wilkins and Pressly ⁶	16†:94	2:10	5:7
Hawes ⁷	15:124	4:11	11:4
Bartley (present report)	19:200	1:18	10:9
Total	100:914	15:64	55:27

*Includes only patients younger than 50 years.

†NR indicates not reported.

‡Four patients had bilateral dacryoliths.

older than 50 years, and the remaining 22 stones were found in 57 patients younger than 50 years. None of the stones occurred in patients whose symptoms were related to trauma. Therefore, lacrimal drainage obstruction was secondary to a dacryolith in 22 of 34 patients (64.7%) younger than 50 years without a history of trauma. Conversely, Herzig and Hurwitz⁴ found that half of the recovered nasolacrimal duct stones were from patients who had had a rhinoplasty, nasal or facial trauma, or lacrimal system scarring after an alkali burn.

Dacryoliths of the lacrimal drainage system may cause recurrent dacryocystitis and symptomatic nasolacrimal duct obstruction. The problem may be chronic or intermittent. Smith and associates⁹ provided evidence that lacrimal drainage symptoms secondary to dacryolithiasis may be differentiated from more common forms of dacryocystitis. They described the syndrome of acute dacryocystic retention as painful nasolacrimal duct obstruction in the absence of pronounced swelling and erythema. Gonnering and Bosniak¹⁰ described a technique of percutaneous dacryolith evacuation as an alternative to dacryocystorhinostomy to treat this entity.

Dacryoliths are suspected to develop from multiple causes. Early reports identified fungal elements within the calculus,^{1,2} whereas another review found hyphae or yeastlike structures in six of ten stones examined.⁵ Several other series^{3,6,7} identified no fungal elements in any of the stones examined histopathologically or by culture, although it should be noted that the

dacryoliths were not always examined with special stains nor were cultures obtained on all specimens. Jones³ commented that regional variations in environment may be responsible for statistical differences between reports and noted that some mycotic diseases were unusual in the cool temperatures of the Pacific Northwest from which he drew his patient base. Similarly, Hawes⁷ mentioned the dry Colorado climate in which he practiced as a factor against fungal stones. Wilkins and Pressly⁶ reported their study from Houston, Texas; a higher incidence of fungal calculi in this warm climate might be assumed but was not verified. A more detailed examination of dacryolith specimens and the epidemiologic characteristics of the patient population would be necessary before generalizing about a fungal cause in nasolacrimal stones.

Herzig and Hurwitz⁴ investigated tear electrolyte levels in patients with dacryoliths, but no correlation was found. The role of cosmetics in stone formation was discounted in one report on the basis that "dacryoliths are reported equally in both sexes."¹¹ This statement is incorrect in that stones are three times more common in females than males (Table). Additionally, our observation of multiple flecks of makeup within a few dacryoliths suggests a possible contributory role.

From a personal communication from Gunderson, Garfin¹² reported a case of an eyelash nidus within a dacryolith of the lacrimal drainage system. Jay and Lee¹³ found an eyelash in the center of one limb of a Y-shaped dacryolith.

Other articles³⁻⁷ reported no cilia within any calculi, although Jones³ did find an eyelash in the mucoid coating surrounding one stone. In our Case 1, the cilium was clearly at the center of the dacryolith with a pseudofollicle housing the foreign body. The rarity of this finding suggests that an eyelash nidus is an infrequent causative agent in nasolacrimal duct stones. Alternatively, it is possible that an eyelash carried into the lacrimal sac may contribute to the initial inflammatory reaction and stone formation and yet later be degraded as the dacryolith enlarges.

Stones of the lacrimal gland ductules have been described infrequently. Baker and Bartley⁸ reported two cases in which the cause of the stone was not apparent. Histopathologic examination of the specimens showed amorphous debris around a nidus of unknown composition with polymorphonuclear leukocytes adherent to the external surface of the stones. Alizarin red stain for calcium was negative in each case.

The findings in Case 2 demonstrate that a stone of the lacrimal gland may remain quiescent for several years without inflammation, infection, or ductular cyst formation.

Eyelashes are frequently observed floating in the tear film or in the conjunctival fornices during routine examinations. Although the finding is of little clinical significance in most cases, such eyelashes should be removed to prevent the potential unusual occurrence of dacryolithiasis.

References

1. Fine, M., and Waring, W. S.: Mycotic obstruction of the nasolacrimal duct (*Candida albicans*). Arch. Ophthalmol. 38:39, 1947.
2. Wolter, J. R., Stratford, T., and Harrell, E. R.: Cast-like fungus obstruction of the nasolacrimal duct. Arch. Ophthalmol. 55:320, 1956.
3. Jones, L. T.: Tear-sac foreign bodies. Am. J. Ophthalmol. 60:111, 1965.
4. Herzig, S., and Hurwitz, J. J.: Lacrimal sac calculi. Can. J. Ophthalmol. 14:17, 1979.
5. Berlin, A. J., Rath, R., and Rich, L.: Lacrimal system dacryoliths. Ophthalmic Surg. 11:435, 1980.
6. Wilkins, R. B., and Pressly, J. P.: Diagnosis and incidence of lacrimal calculi. Ophthalmic Surg. 11:787, 1980.
7. Hawes, M. J.: The dacryolithiasis syndrome. Ophthalmic Plast. Reconstr. Surg. 4:87, 1988.
8. Baker, R. H., and Bartley, G. B.: Lacrimal gland ductule stones. Ophthalmology 97:531, 1990.
9. Smith, B., Tenzel, R. R., Buffam, F. V., and Boynton, J. R.: Acute dacryocystic retention. Arch. Ophthalmol. 94:1903, 1976.
10. Gonnering, R. S., and Bosniak, S. L.: Recognition and management of acute noninfectious dacryocystic retention. Ophthalmic Plast. Reconstr. Surg. 5:27, 1989.
11. Maltzman, B. A., and Favetta, J. R.: Dacryolithiasis. Ann. Ophthalmol. 11:473, 1979.
12. Garfin, S. W.: Etiology of dacryocystitis and epiphora. Arch. Ophthalmol. 27:167, 1942.
13. Jay, J. L., and Lee, W. R.: Dacryolith formation around an eyelash retained in the lacrimal sac. Br. J. Ophthalmol. 60:722, 1976.

The Elastic Properties of the Lens Capsule in Capsulorhexis

Ehud I. Assia, M.D., David J. Apple, M.D., Julie C. Tsai, M.D.,
and Edward S. Lim, M.D.

We investigated the ability of the anterior lens capsule to stretch and allow removal of lens substance and intraocular lens implantation through a continuous circular capsulorhexis. Capsulorhexis of various sizes (2.5 to 7.5 mm) were performed in 50 eyes obtained post mortem from 31 patients. The nucleus and cortex were removed by either phacoemulsification (35 eyes) or manual extracapsular cataract extraction (15 eyes). The opening of the capsule was then gradually enlarged, using a modified caliper with two pins attached to its tips, until the margins were torn. The capsule was torn when the circumference at the time of rupture was 1.6 times larger than the circumference of the original circular capsulotomy or 5.0 times larger than the diameter of the capsulotomy. Manual extraction of a lens nucleus with profile circumference (sagittal or anteroposterior) of 18.0 to 22.0 mm can be performed through a 5.5-mm opening and a 6.0- to 7.0-mm optic intraocular lens (profile circumference of 13.0 to 17.0 mm) can be implanted through a 4.5-mm capsulotomy.

THE CONFIGURATION AND SIZE of an anterior capsulotomy significantly affect the outcome of the cataract operation. Radial capsular tears often result in intraoperative or postoperative lens decentration.^{1,2} Continuous circular capsulorhexis was developed to assure an intact cap-

sulotomy margin and secure capsular intraocular lens implantation.^{3,4} The size and shape of the capsulotomy are determined before lens substance is removed and the intraocular lens is implanted. The diameter of the capsulotomy is always smaller than the diameter of the lens nucleus and is often smaller than the diameter of the intraocular lens optic.

It is well known that the lens capsule has elastic properties.⁵⁻⁹ It is not clear, however, how much a circular continuous capsulotomy can be manipulated to allow safe removal of lens substance and implantation of an intraocular lens while still avoiding tears and maintaining the integrity of the capsulotomy margin. The capsulorhexis technique is used mostly in phacoemulsification procedures. Krag, Thim, and Corydon,⁵ however, studied the stretching capacity of the capsule after capsulorhexis and concluded that nuclear removal can also be safely done by planned extracapsular cataract extraction. We investigated the elasticity of the lens capsule with a continuous circular capsulorhexis to determine what size anterior capsulotomy is needed for lens removal and intraocular lens implantation.

Material and Methods

We studied 50 eyes obtained post mortem from 31 patients (13 men, 15 women, and three of unknown sex). Mean age of the patients was 73.0 ± 9.5 years (range, 52 to 89 years). The eyes were operated on one to seven days after death. Thirty-three eyes (66%) were operated on within three days after death.

The corneas were removed, and the iris was excised down to its root. This permitted clear visualization of the entire anterior capsule, the anterior zonules, and the ciliary processes. A round, continuous capsulorhexis was performed with a bent 26-gauge needle on a 1-ml

Accepted for publication Jan. 25, 1991.

From the Departments of Ophthalmology (Drs. Assia, Apple, Tsai, and Lim) and Pathology (Dr. Apple), Center for Intraocular Lens Research, Storm Eye Institute, Medical University of South Carolina, Charleston, South Carolina. This study was supported in part by a Fulbright scholarship and scholarship from the American Physician Fellowship, Inc. (Dr. Assia), and an unrestricted grant from Research to Prevent Blindness, Inc.

Reprint requests to David J. Apple, M.D., Department of Ophthalmology, Medical University of South Carolina, 171 Ashley Ave., Charleston, SC 29425.

syringe. Sizes ranged from 2.5 to 7.5 mm in diameter. In cases in which the capsulectomy was slightly oval, the largest diameter never exceeded 0.75 mm more than the smallest diameter. In such cases the value obtained was the mean between the longest and shortest diameters of the oval opening. The margins of the nucleus were delineated by hydrodissection and measured with Castroviejo calipers. Lens material was removed by either phacoemulsification (35 eyes) or by manual extraction (15 eyes). In cases of manual extraction the diameter and thickness of the nucleus were measured after it was delivered. The stretch test was performed by using modified Vernier calipers (dial-type with metric scale; accuracy, 0.1 mm). Two pins were attached firmly to the tips of the calipers so that the outer edges of the pins lined up with the inner edges of the caliper tips. The pins were situated so that the diameter between the outer edges corresponded to the reading on the caliper scale. The heads of the pins were carefully introduced into the capsule, and the caliper was opened gradually until the margin of the capsulectomy was torn. The distance

between the tips was then recorded. In three eyes the tear of the anterior capsule did not extend beyond the zonule-free area. This permitted the creation of a second large continuous capsulorhexis with a smooth margin and measurement of its elasticity. A total of 53 measurements were taken.

The circumference of the capsulectomy was calculated as follows: $Cc = \pi \times Dc$ (Cc = circumference of capsulectomy, Dc = diameter of capsulectomy). The circumference at the time of rupture was calculated as follows: $Cr = 2 \times Dr + 2.0$ mm (Cr = circumference at rupture; Dr = diameter at rupture; $+ 2.0$ mm = twice the measured length of contact between the pins and the capsule).

Results

The capsules in all cases stretched extensively before they were torn. Figure 1 demonstrates the manipulations and measurements performed as the capsule is stretched by the cali-

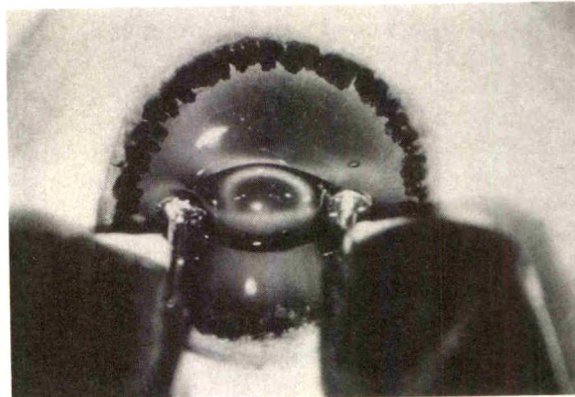
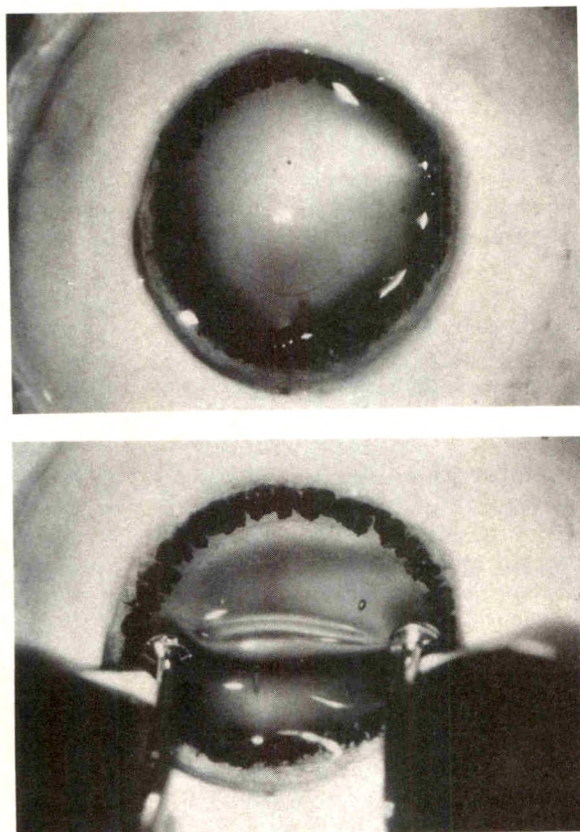


Fig. 1 (Assia and associates). Human eye obtained post mortem, with the cornea and iris removed, showing the capsular stretch test. Top left, A continuous circular capsulorhexis was performed and the lens substance removed. The diameter of the capsulectomy is 4.5 mm; the circumference (Cc) is therefore 14.1 mm. Top right, The two pins attached to the caliper tips were introduced into the capsule through the capsulorhexis. The caliper was then gradually opened. Bottom left, Maximal stretch of the capsular opening immediately before rupture. The diameter is 10.4 mm; the circumference is 22.8 mm. The ratio between circumference just before rupture and the circumference of the capsulectomy at rest ($Cr:Cc$) is 1.62, indicating 62% elasticity of the capsule.

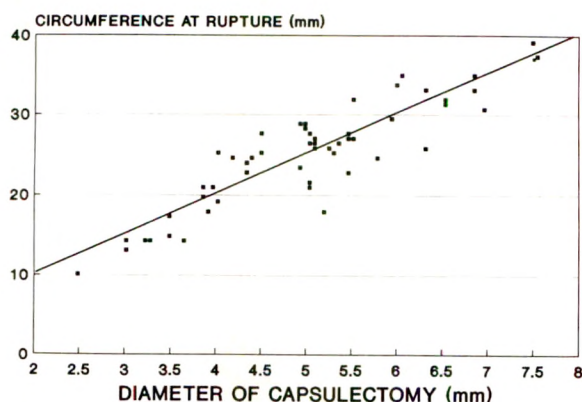


Fig. 2 (Assia and associates). The relationship between the diameter of the anterior capsulotomy (Dc) (abscissa) and the circumference immediately before rupture (Cr) (ordinate) in all cases. The linear relationship is plotted as the rupture line.

per. A highly significant linear correlation was found between the circumference at rupture and the circumference of the capsulotomy ($r = .8956$) (Fig. 2). This relation is expressed as: $Cr = 1.5973 Cc + 0.064$; or modified as: $Cr = 1.6 Cc$; where Cr = circumference at rupture and Cc = circumference of capsulotomy.

The ratio between Cr and Cc in the individual cases (Cr:Cc) was 1.6 ± 0.2 (range, 1.15 to 2.01). If the capsules had no elasticity, this ratio would have been expected to be 1.0. Both the equation and the ratio indicate that the capsule does indeed have elasticity, namely 0.6 mm for each 1.0 mm of capsulotomy or 60% elasticity. Since it is easier clinically for the surgeon to measure the diameter of the capsulotomy rather than to calculate its circumference, the following equation, representing the relation between the circumference at rupture (Cr) and diameter of capsulotomy (Dc), can be used: $Cr = 5.0154 Dc + 0.064$; or modified as: $Cr = 5 Dc$.

To evaluate the opening circumference that is needed to allow lens removal, the dimensions of the lens and nucleus were measured. The mean diameter of the 15 crystalline lenses (before extraction) was 9.76 ± 0.34 mm (range, 9.0 to 10.5 mm). The mean diameter of the extracted nuclei was 7.9 ± 0.54 mm (range, 6.5 to 9.0 mm) and their mean thickness was 3.61 ± 0.25 mm (range, 3.25 to 4.0 mm). During nucleus extraction the capsular opening must be large enough to permit passage of the nucleus at its largest circumference; that is, the central profile or sagittal circumference (Fig. 3). The largest profile circumference of a nucleus was calculat-

ed to be approximately 20.0 mm (range, 18.0 to 22.0 mm). The profile circumference of various types of intraocular lenses were also measured and were 13.0 to 15.0 mm for 6.0-mm optic intraocular lenses and 16.0 to 17.0 mm for 7.0-mm intraocular lenses (relative to optic design and dioptric power). Using this equation and these measurements, one could predict what size of capsulotomy is needed for safe nucleus delivery or intraocular lens implantation. The area below two standard deviations from the rupture line was considered as a relative safe zone (Fig. 4).

The elasticity of the capsule was not affected by the patient's sex, the diameter of the capsulotomy, or the type of operation (phacoemulsification or planned extracapsular cataract extraction). The interval between death and time of examination did not appear to affect the behavior of the capsules. Eyes measured five to seven days after death had similar results to eyes studied one to two days after death. Age played a significant role only in the younger patients (52 to 55 years, five eyes), in whom Cr:Cc ratio was significantly higher than that of the older patients (1.83 and 1.58, respectively; $P = .00395$).

Discussion

The elastic properties of the lens capsule have been recognized since Bowman demonstrated the ability of the capsule to return to its original shape after the lens was swollen with water and then punctured.⁶ The lens capsule is essentially a hypertrophied basement membrane whose unique arrangement of filaments demonstrates some properties of an elastic structure.⁷ Fisher^{6,8,9} and Fisher and Wakely⁷ thoroughly investigated the elastic constants of the human lens capsule and showed that the modulus of elasticity decreases significantly with age. The thickness of the capsule increases until the sixth decade and slightly decreases thereafter. The loss of elasticity is therefore accompanied by a loss of thickness during the aging process. The maximum amount of elongation before rupture was approximately 30%, irrespective of the patient's age.^{6,7}

Fisher⁶ also showed that there is no significant difference in the elasticity of the human lens capsule when measured two or nine days after death. In the rabbit eye, there were no differences in elasticity immediately after death

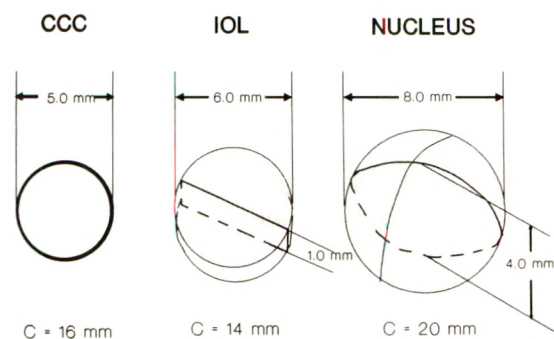


Fig. 3 (Assia and associates). During nucleus extraction or intraocular lens insertion the capsulotomy engulfs the largest profile circumference of the nucleus or intraocular lens (bold line). The circumference (C) of a 5.0-mm circular capsulorhexis is sufficient to permit implantation of a 6.0-mm optic intraocular lens without stretching its margin. To express an 8.0 × 4.0-mm nucleus, however, the capsulorhexis must stretch, and its circumference must increase from 16.0 to 20.0 mm (25%). (CCC indicates continuous circular capsulorhexis, and IOL indicates intraocular lens.)

and after two days.⁶ In our study, too, the elastic properties of the capsule were not affected by the time interval after death, probably because the lens capsule is a membrane and does not contain any living structures. The elasticity of the capsules observed in our study was higher in younger eyes (younger than 55 years) compared to older eyes. In patients older than 60 years, however, age did not significantly alter capsular elasticity.

During extracapsular cataract extraction the anterior capsule is opened to allow removal of lens substance and implantation of an intraocular lens. The diameter of the capsulotomy is smaller than the diameter of the lens nucleus. Therefore, during planned extracapsular cataract extraction and manual lens removal, the nucleus confronts the capsular barrier. Using the capsulotomy technique that creates a sharp edge or serration on the edge of the anterior capsular tear will usually cause a radial tear to occur¹⁰ and passage of the nucleus through the capsular opening is facilitated. A radial tear almost never extends beyond the equator toward the posterior capsule because of the supporting structure of the zonules.¹¹ Nevertheless, the integrity of the capsule is lost and the long-term fixation and stability of the intraocular lens is no longer assured. Capsulorhexis maintains an intact capsule as long as its margin is intact. During lens removal, however, and

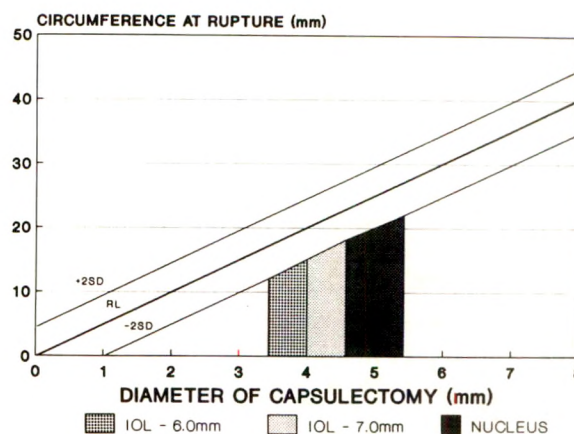


Fig. 4 (Assia and associates). The rupture line (RL) of the capsulotomy was drawn using the modified equation: $Cr = 5.0 \times Dc$ (Cr = circumference at rupture and Dc = diameter of the capsulotomy). The area below two standard deviations ($-2SD$) can be considered as the surgical relative safe zone. Based on our experimental data, an intraocular lens with a 6.0-mm optic can be implanted through a 4.0-mm capsulotomy. A 7.0-mm optic can be inserted through a 4.5-mm capsulotomy. A nucleus with mean dimensions of 8.0 × 4.0 mm can be delivered through an opening of 5.5 mm without tearing the margin of the capsulorhexis (see Fig. 3). (IOL indicates intraocular lens.)

often during intraocular lens implantation, the edges have to be stretched to enlarge the opening. In the case of a small opening, when the lens is removed by pressing the globe, an increase of the intraocular pressure occurs, and the force needed to enlarge the elastic opening might exceed that which will rupture the zonules. Zonular rupture and even inadvertent intracapsular cataract extraction might thus occur. In cases where planned extracapsular cataract extraction is done in association with continuous circular capsulorhexis, the margins of the capsulotomy may rupture in an uncontrolled manner. Some surgeons advocate making relaxing incisions (episiotomies) before the lens is removed.^{12,13} A creation of artificial radial cuts, however, is contrary to the surgeon's efforts and desire to perform a continuous smooth-edged capsulotomy that will maintain an intact capsule. A large anterior capsulotomy may be attempted (more than 7 mm), but it may be directed outward by the zonules or may cause damage to the anterior zonules. The anterior zonules are attached 1.25 to 2.0 mm anterior to the equator, thus leaving only a 6.5- to 7.0-mm zonule-free area. Other investigators

have suggested that the zonule-free area decreases with age, and in the eighth decade it is often 6.0 mm and less.¹⁴ In rare cases, zonule-free areas as small as 1.8 to 2.1 mm were reported.¹⁵ In all of our cases, however, a zonule-free area of 6.5 mm has been identified under high-power magnification.

Our results indicate that the capsular opening can be enlarged by 0.6 mm for each 1.0 mm of capsulectomy before it ruptures. If one considers two standard deviations below the rupture line as a zone of safety, it follows that a large nucleus can be delivered through a 5.5-mm opening without tearing of the capsule (Fig. 4). We would, however, recommend an opening of 6.0 to 6.5 mm, in which less force is needed to stretch the capsule and deliver the nucleus. Assia and associates¹⁰ demonstrated in a controlled laboratory study that a 6.0-mm capsulorhexis maintained its integrity in all cases, whereas other common types of capsulectomies were always associated with radial tears. To reduce the risks of tearing zonules it is probably best to deliver the nucleus by injection of fluid between the nucleus and the cortex (hydrodissection) followed by manual extraction of the nucleus. With this technique the fluid pushes the posterior capsule backward as the nucleus is forced forward, and the zonules are subjected to minimal stress. In the case of lens removal by phacoemulsification, the diameter of the capsulectomy can be reduced to as small as 4.0 to 4.5 mm and still permit safe implantation of an intraocular lens. A smaller capsulectomy probably would not have any advantage since the anterior capsule usually opacifies. Also, if the central opening decreases in diameter secondary to capsular fibrosis and contraction, the optical area would be unacceptably reduced.

References

1. Apple, D. J., Park, S. B., Merkley, K. H., Brems, R. N., Richards, S. C., Langley, K. E., Piest, K. L., and Isenberg, R. A.: Posterior chamber intraocular lenses in a series of 75 autopsy eyes. Part I. Loop location. *J. Cataract Refract. Surg.* 12:358, 1986.
2. Hansen, S. O., Tetz, M. R., Solomon, K. D., Borup, M. D., Brems, R. N., O'Morchoe, D. J. C., Bouhaddou, O., and Apple, D. J.: Decentration of flexible loop posterior chamber intraocular lenses in a series of 222 postmortem eyes. *Ophthalmology* 95:344, 1988.
3. Neuhann, T.: Theorie Und Operationstechnik der Kapsulorhexis. *Klin. Monatsbl. Augenheilkd.* 190:542, 1987.
4. Gimbel, H. V., and Neuhann, T.: Development, advantages and methods of the continuous circular capsulorhexis technique. *J. Cataract Refract. Surg.* 16:31, 1990.
5. Krag, S., Thim, K., and Corydon, L.: The stretching capacity of capsulorhexis. An experimental study on animal cadaver eyes. *Eur. J. Implant Refract. Surg.* 2:43, 1990.
6. Fisher, R. F.: Elastic constants of the human lens capsule. *J. Physiol.* 201:1, 1969.
7. Fisher, R. F., and Wakely, J.: The elastic constants and ultrastructural organization of a basement membrane (lens capsule). *Proc. R. Soc. Lond. [Biol.]* 193:335, 1976.
8. Fisher, R. F.: The influence of age on some ocular basement membranes. *Eye* 1:184, 1987.
9. ———: The structure and function of basement membrane (lens capsule) in relation to diabetes and cataract. *Trans. Ophthalmol. Soc. U.K.* 104:755, 1985.
10. Assia, E. I., Apple, D. J., Barden, A., Tsai, J. C., Castaneda, V. E., and Hoggatt, J. S.: An experimental study comparing various anterior capsulectomy techniques. *Arch. Ophthalmol.* In press.
11. Assia, E. I., Apple, D. J., Tsai, J. C., and Morgan, R. C.: Mechanism of radial tear formation and extension after anterior capsulectomy. *Ophthalmology*. In press.
12. Almallah, O. F.: Capsulorhexis complications with planned extracapsular cataract extraction. *J. Cataract Refract. Surg.* 15:232, 1989.
13. Maher, J. F.: Nucleus expression after capsulorhexis. *J. Cataract Refract. Surg.* 14:693, 1989.
14. Stark, W. J., and Streeten, B.: The anterior capsulectomy of extracapsular cataract extraction. *Ophthalmic Surg.* 15:911, 1984.
15. Koch, D. D., and Liu, J. F.: Zonular encroachment on the anterior capsular zonular-free zone. *Am. J. Ophthalmol.* 106:491, 1988.

Magnetic Resonance Imaging Evaluation of Uveal Tumors

William R. Raymond IV, M.D., Devron H. Char, M.D., David Norman, M.D.,
and Eugene E. Protzko, M.D.

We detected seven tumors with magnetic resonance imaging, which demonstrate some of the uses and limitations of this diagnostic technique. In one patient, the correct diagnosis of extraocular extension was demonstrated with magnetic resonance imaging when both clinical and ultrasonographic data were not diagnostic. In another case, an extremely small area of extraocular extension was detected with ultrasound evaluation but was not noted on magnetic resonance imaging. Magnetic resonance imaging is highly reliable in the detection of intraocular tumors. In pigmented uveal melanomas it is both sensitive and highly specific. In amelanotic processes magnetic resonance imaging can identify a mass but cannot always adequately characterize it. Further experience will be necessary to determine the proper role of magnetic resonance imaging in the evaluation of uveal tumors.

IT IS SOMETIMES DIFFICULT to establish the correct diagnosis of an atypical uveal lesion.¹ Enucleations of eyes with suspected uveal melanomas that have a simulating lesion on histologic examination are uncommon; however, some incorrect diagnoses still occur even after clinical examination, fluorescein angiography, ultrasonography, or fine-needle aspiration biopsy.²⁻⁵ The diagnostic accuracy of ancillary tests in unusual cases is uncertain.

Magnetic resonance imaging of pigmented

uveal melanomas has a characteristic signal secondary to the paramagnetic properties of melanin.⁶⁻¹² Some investigators have observed that magnetic resonance signal characteristics are diagnostic and have suggested that magnetic resonance imaging might be helpful in difficult cases.⁶⁻¹¹ In addition to tumor characterization, magnetic resonance imaging can improve delineation of tumor margins and detection of extraocular extension.^{7,11} We studied seven cases that demonstrate some advantages and limitations of magnetic resonance imaging in the evaluation of uveal tumors.

Case Reports

Case 1

An 85-year-old woman underwent an uncomplicated extracapsular cataract extraction. Postoperatively, she noted progressively decreased vision, which was attributed initially to pseudophakic cystoid macular edema. Further examination disclosed a large choroidal mass, which was thought by the referring retinal consultant to be a serous choroidal detachment. When this lesion failed to resolve, the patient was referred for ocular oncologic examination. Fundus examination showed a large pigmented ciliochoroidal mass that involved more than five clock hours and was associated with an exudative hemiretinal detachment. The clinical appearance was most consistent with a ciliochoroidal melanoma. Findings commonly associated with serous or hemorrhagic choroidal detachments, such as anterior displacement of the iris-lens diaphragm or breakthrough hemorrhage, were absent.

The ultrasound pattern was not entirely diagnostic. A ciliochoroidal mass was noted with an internal quiet zone and evidence of choroidal excavation. The internal echoes on quantitative echography dropped immediately almost to baseline. There were no spontaneous pulsations, and maximum tumor thickness was 12.8

Accepted for publication Jan. 23, 1991.

From the Departments of Ophthalmology, Ocular Oncology Unit (Drs. Raymond, Char, and Protzko), Radiation Oncology (Dr. Char), Radiology and Neuroradiology (Dr. Norman), and the Francis I. Proctor Foundation (Dr. Char), University of California, San Francisco, California. This study was supported in part by National Institutes of Health grant EY07504, and by unrestricted grants from That Man May See, Research to Prevent Blindness, Inc., and the Beal Foundation.

Reprint requests to Devron H. Char, M.D., Ocular Oncology Unit, P.O. Box 0730, UCSF, San Francisco, CA 94143.

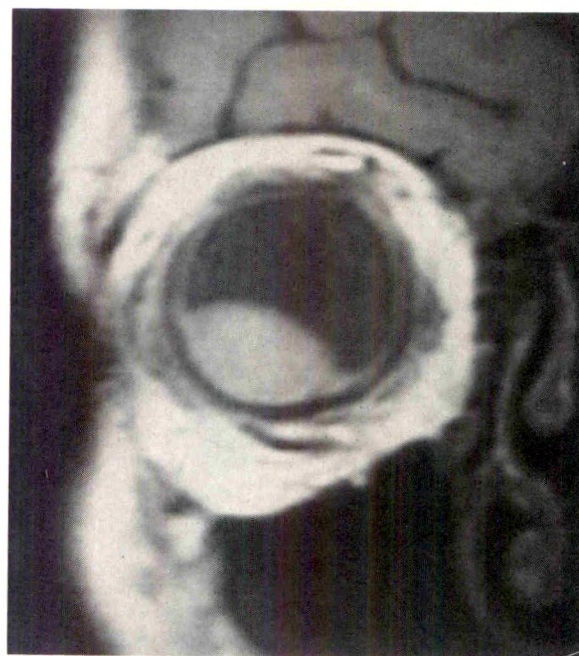


Fig. 1 (Raymond and associates). A uveal melanoma with an exudative detachment. On 4.0-mm thick coronal (top left) and axial (top right) 3-in surface coil short TR/TE images (800 msec/20 msec) the lesion is higher in signal intensity than both vitreous and mid intensity brain tissue. On the long TR/TE images (2,000 msec/80 msec) (bottom left) the tumor intensity is much lower than vitreous and slightly lower in intensity than normal brain. These signal characteristics are typical for melanotic melanoma. The circumferential high signal intensity collection on the short TR/TE image maintains a high signal on the long TR/TE image, which indicates an exudative detachment rather than choroidal extension of the tumor.

mm. Magnetic resonance findings were typical for a pigmented uveal melanoma with an exudative detachment. The lesion was well circumscribed and exhibited high-intensity signal relative to vitreous and brain on short TR (repetition time)/TE (echo time) (T_1) images and was isointense to low-intensity signal on long TR/TE (T_2) images (Fig. 1).

The eye was enucleated, and histopathologic

examination disclosed a spindle-cell malignant melanoma.

Case 2

A 61-year-old man had contralateral amblyopia and an ipsilateral small melanoma that extended to the lateral edge of the fovea. A small amount of subretinal fluid, orange pigment, and drusen were present. The mass was

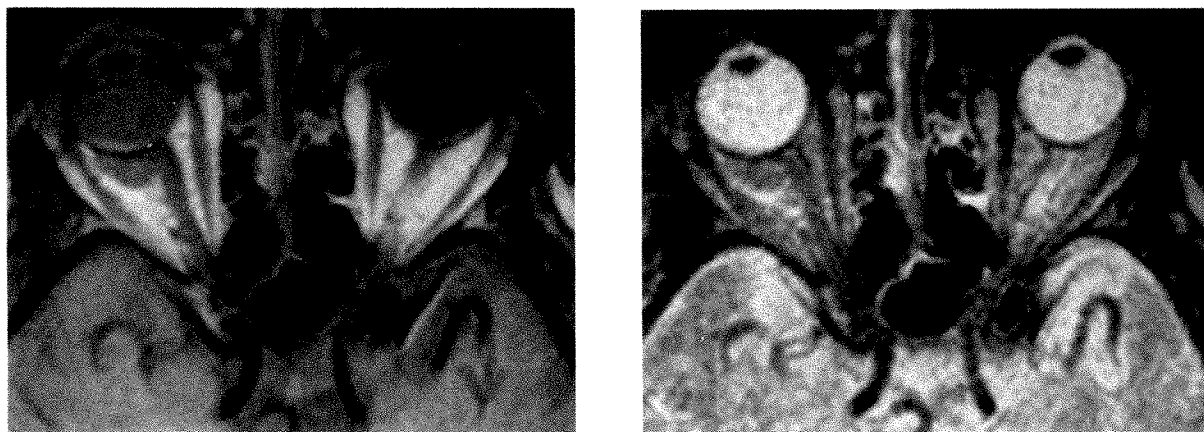


Fig. 2 (Raymond and associates). Axial 5.0-mm thick short TR/TE (600 msec/20 msec) (left) and long TR/TE (2,000 msec/100 msec) (right) images acquired with a head coil. A 15.0 × 5.0-mm well-circumscribed episcleral mass of the right globe displaces the distal optic nerve to the left. The lesion was slightly hyperintense relative to vitreous on short TR/TE images but hypointense to vitreous and slightly hypointense to brain on the long TR/TE image. Tumor signal characteristics are compatible with melanotic melanoma.

10.5 × 9.0 × 3.5 mm. Tumor growth was documented, and the eye was treated with ¹²⁵I brachytherapy.

Early tumor regression was noted. Five months later decreased vision and radiation optic neuropathy were observed. The tumor had decreased in size to approximately 10.5 × 9.0 × 2.8 mm. An unusual homogeneous area posterior to the sclera was noted on ultrasound. In consultation, several ocular oncologists believed that this area represented a benign post-treatment change, although an extraocular extension of melanoma could not be ruled out.

Clinically, posterior tumor extension was believed unlikely, since at plaque placement five months previously no extraocular extension was noted, the intraocular tumor had shrunk, the sclera received exponentially more irradiation than the tumor apex, and treatment replanning disclosed adequate radiation delivery. One month later a new area of exudative detachment inferior to the tumor was seen. Ultrasound showed enlargement of the retroorbital mass.

Magnetic resonance imaging disclosed a well-circumscribed 15.0 × 5.0-mm retrobulbar lesion (Fig. 2). It was hyperintense relative to vitreous but isointense with brain on both the short TR/TE and first echo of the long TR/TE images. The lesion was hypointense to both vitreous and brain on long TR/TE image. Magnetic resonance findings were believed to be diagnostic for extraocular extension of the uveal melanoma.

Orbital exploration and fine-needle aspira-

tion biopsy disclosed melanoma. An eyelid-sparing exenteration was performed, and on histopathologic examination a mixed-cell malignant melanoma was noted (Fig. 3). There was no evidence of extension of the tumor through a suture tract at the site of ¹²⁵I plaque placement as the cause of tumor extension.

Case 3

A 61-year-old woman with a suspected melanoma was referred by a retinal specialist. The patient noted decreased vision in the right eye approximately two months before the initial examination, when she inadvertently covered her left eye. A dense vitreous hemorrhage was found. On B-scan ultrasonography, a retinal detachment without an apparent associated mass was noted. A pars plana vitrectomy was performed, and a large pigmented choroidal mass with surrounding subretinal hemorrhage was discovered. She was referred to us for further examination and therapy.

Our examination disclosed visual acuity of hand motions in the right eye. Examination of the anterior segment showed bilateral cataractous lens changes and injection of the conjunctiva and sclera as a consequence of her recent surgery. Results of ophthalmoscopic examination of the left eye were normal. Examination of the right fundus disclosed a core vitrectomy with a lesion overlying the disk that involved the macula. There was subretinal hemorrhage with a discrete pigmented lesion with a collar button configuration. The tumor measured 17.0 × 13.0 × 6.8 mm (Fig. 4). No associated retinal

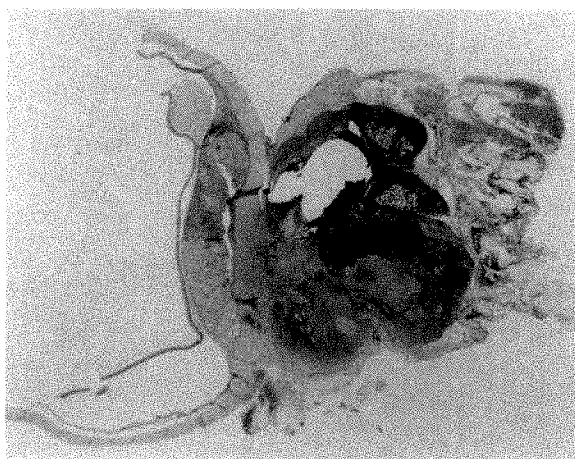


Fig. 3 (Raymond and associates). Gross histopathologic specimen demonstrating extraocular extension of uveal melanoma shown in Figure 2.

detachment, orange pigment, or overlying drusen were present.

The ultrasound pattern was not diagnostic for melanoma. No acoustic quiet zone, choroidal excavation, or orbital shadowing were seen. On quantitative echography this appeared to be a heterogenous lesion consistent with an extramacular disciform process. Fluorescein angiography showed only blockage of fluorescence. The magnetic resonance imaging scan disclosed a pattern typical for an extramacular disciform process. On short TR/TE images the lesion was of high intensity compared to vitreous. On long TR/TE images it exhibited marked reduction in signal intensity compared to vitreous. This marked shortening of T_1 and T_2 relaxation times would be unusual for a uveal melanoma and more compatible with intracellular methemoglobin (Fig. 5). Serial clinical and ultrasonographic examination demonstrated almost entire resolution of this extramacular disciform process.

Case 4

A 50-year-old woman was referred for examination of a left ciliochoroidal mass with a secondary retinal detachment. The patient had noted fuzzy vision approximately six months previously. At our examination, visual acuity was 20/25-. An afferent pupillary defect was present. Slit-lamp examination disclosed two areas of apparent extrascleral pigmentation with an enlarged episcleral vessel between the 6 o'clock and 8 o'clock meridians. The angle

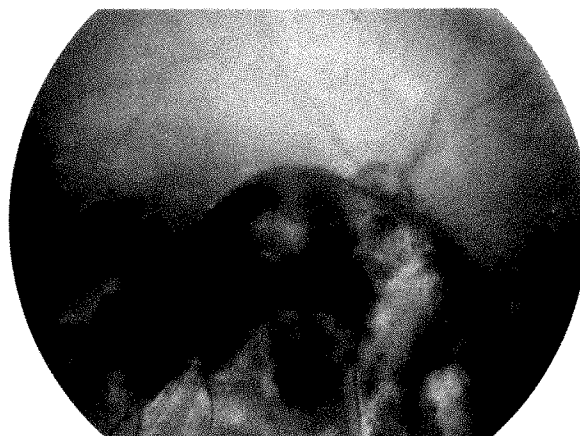


Fig. 4 (Raymond and associates). Case 3, referred with a uveal melanoma. There was vitreous hemorrhage and intralesional hemorrhage. Serial observation demonstrated disappearance of this extramacular disciform process.

was open, and no tumor was seen. A ciliochoroidal pigmented mass that extended posteriorly to within 7.5 mm of the optic disk involved almost the entire inferonasal quadrant. Subretinal hemorrhage and exudative retinal detachment were noted. The tumor dimensions were 17.0 × 12.0 × 7.0 mm. The ultrasound pattern was consistent with melanoma, and on B scan an area of probable scleral penetration was seen. Magnetic resonance imaging was consistent with melanoma, but no extraocular extension was demonstrated. Histopathologic examination disclosed a mixed-cell ciliochoroidal melanoma, with a small area of localized, encapsulated extraocular extension.

Case 5

A 51-year-old woman noted the onset of floaters and decreased vision in her left eye. Visual acuity was 20/20 in each eye, and results of the anterior segment examination were normal. The entire inferior left fundus was darkly pigmented. A sharp line of demarcation separated this area from the normal-appearing superior fundus (Fig. 6). The inferior retina was flat except for an area at the temporal equator that was 10.5 × 10.0 × 6.3 mm and had indistinct margins. A collar button configuration was present without subretinal fluid.

On ultrasound, the elevated portion of this lesion was consistent with melanoma. Fluorescein angiography showed intrinsic vascularity and hot spots within the mass; only hypofluo-

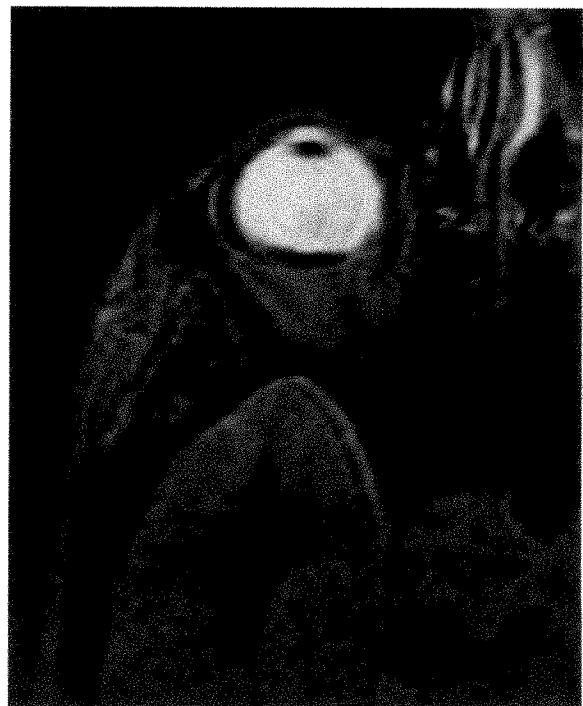


Fig. 5 (Raymond and associates). Axial 3.0-mm images of lesion shown in Figure 4 demonstrate a lesion with high signal relative to vitreous on short TR/TE (600 msec/20 msec) images and low signal intensity on long TR/TE images (2,000 msec/80 msec). The marked T_2 shortening would be most unusual for melanoma and more compatible with intracellular methemoglobin.

rescence, probably caused by blockage, was noted in the flat areas of abnormal pigmentation. The magnetic resonance signal intensities were consistent with melanoma. The lesion had high signal intensity relative to vitreous and brain on short TR/TE images and low signal intensity relative to vitreous on long TR/TE images. No other abnormalities of the inferior fundus were detected. Histologic examination disclosed a mixed-cell melanoma in the elevated area. A benign process accounted for pigmentation of the inferior retina including retinal pigment epithelial hyperplasia and pigmented macrophages.

Case 6

A 27-year-old woman had blurred vision in the right eye. An amelanotic posterior mass was found, and she was referred to a retinal specialist. Based on clinical examination and fluorescein angiography, a small choroidal hemangioma was diagnosed. She was treated with blue-green argon laser and was lost to subsequent examination for approximately eight years. Upon her return, she had best-corrected

visual acuity of counting fingers at 2 feet and a large nonpigmented, nodular tumor located in the macula. She was referred for examination and treatment of a recurrent uveal tumor.

Results of the anterior segment examination, ocular motility, and intraocular pressure were all normal. A macular amelanotic tumor measuring $12.0 \times 12.0 \times 10.8$ mm was noted. Subretinal fluid was noted directly over the lesion without a dependent exudative detachment. Ultrasound and fluorescein angiography were consistent with melanoma as was the magnetic resonance imaging. Magnetic resonance signal intensity differed from pigmented melanomas. It was isointense with brain on both short and long TR/TE images. There was high signal intensity relative to vitreous on short TR/TE images, but it was not as bright as usually observed with uveal melanomas.

Case 7

A 56-year-old woman noted the acute onset of decreased visual acuity in the right eye. Examination by an optometrist disclosed a retinal detachment, and she was referred to an

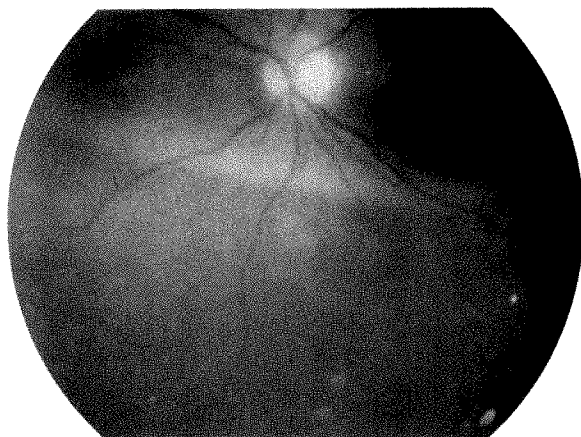


Fig. 6 (Raymond and associates). Case 5. Area of pigmentation away from the main melanoma mass. The nature of this pigmentation was uncertain.

ophthalmologist, who found an exudative retinal detachment and a choroidal mass. The patient had a 35-pack year smoking history and had vocal chord polyps.

Examination disclosed best-corrected visual acuity of 20/20. The anterior segment was unremarkable. The left fundus was normal, but examination of the right fundus disclosed a large, lightly pigmented uveal tumor measuring $20.0 \times 14.0 \times 12.5$ mm. This mass extended both anterior and posterior to the equator, came within 3.0 mm of the disk, and partially overhung the fovea. Chest x-ray disclosed a large mass in the left lower lobe that was confirmed by lung biopsy to be a primary adenocarcinoma. The ocular ultrasound pattern was consistent with a melanoma. The magnetic resonance pattern was typical for a pigmented uveal melanoma.

A fine-needle aspiration biopsy of the uveal tumor showed melanoma. Shortly after enucleation, the patient underwent a successful left lower lobectomy. No evidence of ocular or other metastatic disease was found 18 months later.

Discussion

Several studies have reported magnetic resonance imaging features of intraocular tumors.⁶⁻¹² Pigmented uveal melanomas have relatively short T_1 and T_2 relaxation times, high signal intensity compared to vitreous on short TR/TE images, and reduced signal on long

TR/TE images.⁷⁻¹⁰ This pattern is attributed to the paramagnetic properties of melanin.⁸ Magnetic resonance imaging differentiates pigmented uveal melanomas from other simulating lesions; however, there is a scarcity of data in atypical cases.^{9,13,14}

In this study, magnetic resonance imaging detected all uveal melanomas, including three cases that had atypical features. One patient was referred with a postcataract hemorrhagic choroidal detachment. Choroidal detachments most commonly develop when intraoperative hypotony is combined with postoperative inflammation. Shallowing of the anterior chamber caused by forward shift of the iris-lens diaphragm is a diagnostic clue but is often absent in patients with posterior chamber implants.¹⁵⁻¹⁹ In this case the diagnosis of a uveal melanoma was confirmed with both ultrasound and magnetic resonance imaging.

The patient described in Case 7 had a long history of smoking, vocal cord polyps, and a large left pulmonary primary adenocarcinoma. The appearance of the uveal tumor on clinical, ultrasound, fluorescein angiographic, and magnetic resonance imaging criteria was consistent with a uveal melanoma; that diagnosis was confirmed by fine-needle aspiration biopsy. We have examined many patients with a history of systemic malignancy who have had a misdiagnosis of a metastatic uveal mass, and we have also seen patients with metastatic tumors in the eye that were misdiagnosed as uveal melanomas. Kindy-Degnan, Char, and Kroll²⁰ reported that 53 of 627 (8%) patients with choroidal or ciliary body melanomas had a second, systemic noncutaneous malignant disorder. In a case report by Simons, Straatsma, and Foos,⁴ a metastatic adenocarcinoma was misdiagnosed as a choroidal melanoma despite ultrasound, fluorescein angiographic, and magnetic resonance imaging data.

A major diagnostic limitation of magnetic resonance imaging for uveal tumor diagnosis is in the evaluation of amelanotic mass lesions. It can be difficult to differentiate an amelanotic uveal melanoma, choroidal metastasis, or a choroidal hemangioma on both clinical and magnetic resonance imaging criteria. Peyster and associates⁷ observed high signal on short TR/TE images and an isointense pattern on long TR/TE images in three choroidal hemangiomas. In contrast, Mafee and associates⁸ noted the opposite in one case. The fluorescein angiographic pattern for hemangioma may be diagnostic; however, we have treated patients

with these fluorescein findings who were histologically shown to have uveal melanomas.^{2,21} The accuracy of magnetic resonance imaging for amelanotic uveal tumor diagnosis does not appear to be better than less expensive imaging techniques, such as ultrasonography. In Case 6, the magnetic resonance signal characteristics were not pathognomonic for melanoma. The T_1 and T_2 shortening were not as marked as usually seen. The lesion was compatible with a melanoma but could not be distinguished from a metastatic choroidal tumor on magnetic resonance imaging. Amelanotic melanomas are often not distinguishable from other uveal neoplasms on magnetic resonance imaging.²² Peyster and associates⁷ noted a characteristic signal pattern in 51 of 55 uveal melanomas. The remaining four lesions were amelanotic; on short TR/TE images these exhibited high signal in three patients and isointense signal in one. Peyster and associates⁷ described four choroidal metastases as isointense to vitreous on short TR/TE images and hypointense on long TR/TE studies. In a single case of metastatic breast carcinoma, Mafee and associates⁸ noted high signal intensity on both short and long TR/TE images.

Case 3 demonstrates a potential use of magnetic resonance imaging in the evaluation of atypical pigmented uveal tumors. The patient was referred because of a uveal melanoma. The magnetic resonance pattern on both short and long TR/TE images demonstrated marked shortening of T_1 and T_2 relaxation times. It is most unusual for a melanoma to produce this degree of T_2 shortening or signal reduction. The signal alterations were more compatible with a subacute hemorrhagic process.¹⁴ We have examined two additional patients with an identical magnetic resonance imaging pattern who had extramacular disciform lesions. The eye of one of these two patients was enucleated at another institution because of the incorrect diagnosis of a uveal melanoma.

The relative diagnostic accuracies of magnetic resonance imaging and ultrasound are uncertain. A number of cases with incorrect diagnoses that had been evaluated with ultrasound and other techniques have previously been reported.^{1-5,23} Some magnetic resonance false diagnoses have also occurred. Simons, Straatsma, and Foos⁴ reported a single case of a uveal mass that had a high signal on a short TR/TE image that proved to be a metastatic adenocarcinoma. Long TR/TE images, however, were not obtained. Mafee and associates¹⁰ reported a meta-

static breast carcinoma that had high signal intensity and short TR/TE image, but unlike a pigmented melanoma it remained high in signal intensity on T_2 -weighted images. As demonstrated by Case 6, amelanotic tumors are difficult to differentiate with magnetic resonance scans and are probably better differentiated with ultrasonography.

A second potential use of magnetic resonance imaging is to demarcate the intraocular and extraocular limits of a tumor. In Case 4, there was a flat, heavily pigmented area that involved almost the entire inferior half of the fundus. The elevated, less pigmented mass temporally was consistent with a choroidal melanoma, but it was uncertain whether the flat pigmentation was part of a diffuse melanoma, subretinal hemorrhage, retinal pigment epithelial hyperplasia, or caused by pigmented macrophage deposition.²⁰ A review of the medical records indicated that this abnormal pigment was not documented on previous ophthalmic examinations. The magnetic resonance imaging pattern was consistent with a discrete tumor, and this was concordant with the histologic findings. Possibly the flat area of pigment was not detected on magnetic resonance imaging because it was thin. The lack of short TR/TE images in the coronal plane also resulted in a failure to avoid the partial-volume artifact inherent in 3.0-mm axial images.

In Case 2, there was an enlarging retrobulbar mass noted on ultrasonography in an area previously treated with ^{125}I irradiation. The interpretation of the ultrasound in this case was partially predicated on the clinical data. A number of ocular oncologists believed that this process was most likely not caused by extraocular extension of the tumor. During placement of the ^{125}I plaque, there was no evidence of extraocular extension of the melanoma. The radiation dose appeared to be sufficient to control the intraocular tumor, and this newly involved area was within the radiation field. Brachytherapy provides exponentially more radiation to the scleral surface as compared to the tumor apex, so it was believed to be likely that the retrobulbar change was caused by radiation or surgical damage. The magnetic resonance scan provided us with the correct diagnosis of extraocular extension of melanoma, which was confirmed by fine-needle aspiration biopsy before performing an eyelid-sparing exenteration.

De Keizer, Vielvoye, and de Wolff-Rouendaal¹¹ postulated that the quality of magnetic resonance scans should be sufficient to distin-

guish among tumor, scleral, and orbital tissues. Our magnetic resonance data show delineation of local tumor extension can be limited. One case with obvious extraocular extension was detected on magnetic resonance imaging and not definitively diagnosed with ultrasound. In another case with a smaller extension, ultrasound detected the spread, whereas magnetic resonance imaging did not. Magnetic resonance imaging was accurate in the delineation of the intraocular boundaries of the tumor in a heavily pigmented quadrant where the clinical question was whether the patient had a discrete lesion or diffuse melanoma.

Thin-section magnetic resonance imaging is reliable in the detection of intraocular tumors and definition of their boundaries. Its diagnostic accuracy in comparison to ultrasonography is uncertain. In pigmented uveal tumors magnetic resonance imaging appears to be highly sensitive and specific. In amelanotic tumors or inflammatory processes magnetic resonance will identify the mass but cannot always accurately characterize it.

Further experience will be necessary to determine the proper role of magnetic resonance imaging in the evaluation of uveal tumors. We do not routinely obtain magnetic resonance imaging scans in patients with uveal melanomas. It is a relatively expensive study. We use magnetic resonance imaging scans in patients with atypical uveal tumors, patients with known metastatic tumors to the choroid, and those in whom there is the possibility of extraocular tumor extension. The rationale for this approach is threefold. First, in atypical cases an additional noninvasive assay may be diagnostic before resorting to fine-needle aspiration biopsy. Second, in patients with uveal metastases the status of the contiguous central nervous system is crucial for treatment planning, and magnetic resonance imaging is the assay of choice in that setting. Third, this study has demonstrated that magnetic resonance imaging may add valuable information in some cases of extraocular tumor extension.

References

1. Char, D. H., Stone, R. D., Irvine, A. R., Crawford, J. B., Hilton, G. F., Lonn, L. I., and Schwartz, A.: Diagnostic modalities in choroidal melanoma. *Am. J. Ophthalmol.* 89:223, 1980.
2. Ferry, A. P.: Lesions mistaken for malignant melanoma of the posterior uvea. *Arch. Ophthalmol.* 72:463, 1964.
3. Smith, P. A., Damato, B. E., Ko, M.-R., and Lyness, R. W.: Anterior uveal neurilemmoma. A rare neoplasm simulating malignant melanoma. *Br. J. Ophthalmol.* 71:34, 1987.
4. Simons, K. B., Straatsma, B. R., and Foos, R. Y.: False positive diagnosis of choroidal melanoma by magnetic resonance imaging. *Ann. Ophthalmol.* 19:457, 1987.
5. Liu, K. R., Peyman, G. A., Mafee, M. F., and Yu, D. Y.: False positive magnetic resonance imaging of a choroidal nevus simulating choroidal melanoma. *Int. Ophthalmol.* 13:265, 1989.
6. Peyster, R. G., Shapiro, M. D., and Haik, B. G.: Orbital metastasis. Role of magnetic resonance imaging and computed tomography. *Radiol. Clin. North Am.* 24:647, 1987.
7. Peyster, R. G., Augsburger, J. J., Shields, J. A., Hershey, B. L., Eagle, R., and Haskin, M. E.: Evaluation with MR imaging. *Radiology* 168:773, 1988.
8. Mafee, M. F., Peyman, G. A., Peace, J. H., Cohen, S. B., and Mitchell, M. W.: Magnetic resonance imaging in the evaluation and differentiation of uveal melanoma. *Ophthalmology* 94:341, 1987.
9. Haik, B. G., Saint Louis, L., Smith, M. E., Ellsworth, R. M., Deck, M., and Friedlander, M.: Magnetic resonance imaging in choroidal tumors. *Ann. Ophthalmol.* 19:218, 1987.
10. Mafee, M. F., Peyman, G. A., Grisolano, J. E., Fletcher, M. E., Spignos, D. C., Wehrli, F. W., Rasouli, F., and Capek, V.: Malignant uveal melanoma and simulating lesions. MR imaging evaluation. *Radiology* 160:773, 1986.
11. de Keizer, R. J. W., Vielvoye, G. J., and de Wolff-Rouendaal, D.: Nuclear magnetic resonance imaging of intraocular tumors. *Am. J. Ophthalmol.* 102:438, 1986.
12. Zimmerman, R. A., Bilaniuk, L. T., Yanoff, M., Schenck, J. F., Hart, H. R., Foster, T. H., Edelstein, W. A., Bottomley, P. A., Redington, R. W., and Hardy, C. J.: Orbital magnetic resonance imaging. *Am. J. Ophthalmol.* 100:312, 1985.
13. Okabe, H., Kiyosawa, M., Mizuno, K., Yamada, S., and Yamada, K.: Nuclear magnetic resonance imaging of subretinal fluid. *Am. J. Ophthalmol.* 102:640, 1986.
14. Pepsin, S. R., Katz, L. J., Augsburger, J. J., Chien, A. M., and Eagle, R. C., Jr.: Acute angle-closure glaucoma from spontaneous massive hemorrhagic retinal or choroidal detachment. *Ophthalmology* 97:76, 1990.
15. Brubaker, R. F., and Pederson, J. E.: Ciliochoroidal detachment. *Surv. Ophthalmol.* 27:281, 1983.
16. Chess, J., and Marcus, D.: Persistent choroidal detachment. *Br. J. Ophthalmol.* 71:720, 1987.
17. Slusher, M. M.: Pseudophakic choroidal detachment with cyclodialysis cyst. *Ophthalmic Surg.* 18:191, 1987.
18. Berke, S. J., Bellows, R., Shingleton, B. J.,

Richter, C. U., and Hutchinson, B. T.: Chronic and recurrent choroidal detachment after glaucoma filtering surgery. *Ophthalmology* 94:154, 1987.

19. Brockhurst, R. J.: Nanophthalmos with uveal effusion. *Arch. Ophthalmol.* 93:1289, 1975.

20. Kindy-Degnan, N., Char, D. H., and Kroll, S. M.: Coincident systemic malignant disease in uveal melanoma patients. *Can. J. Ophthalmol.* 24:204, 1989.

21. Gomori, J. M., Grossman, R. I., Shields, J. A., Augsburger, J. J., Joseph, P. M., and DeSimeone, D.: Choroidal melanomas. Correlation of NMR spectroscopy and MR imaging. *Radiology* 158:443, 1986.

22. Atlas, S.: MRI of the orbit. Current status. *Magn. Reson. Imaging* 5:1, 1987.

23. Char, D. H.: *Clinical Ocular Oncology*. New York, Churchill-Livingstone, Inc., 1989, p. 93.

OPHTHALMIC MINIATURE

This sixteen-year-old girl, who was attending school in Bordeaux, was quite suddenly afflicted by one of the most dreaded diseases of the eye. Dr. Bermond, the famous ophthalmologist of the University of Bordeaux, diagnosed retinal detachment of both eyes leading to inevitable total blindness. The prognosis was soon confirmed. In a few weeks the blood-suffused veil had wholly darkened the comely girl's eyes and the shadow grew deeper after each awakening. As is common in these desperate cases the family struggled and struggled and would not submit to the cruelty of fate. The blind girl was tormented by a hundred attempts at cure. Since none helped, it was decided at last to repair to Paris and consult scientific luminaries there.

Ludwig Lewisohn, *The Song of Bernadette*
New York, The Viking Press, 1942, p. 347

AMERICAN JOURNAL OF OPHTHALMOLOGY®

FRANK W. NEWELL, *Publisher and Editor-in-Chief*
Suite 1415, 435 North Michigan Ave., Chicago, Illinois 60611

EDITORIAL BOARD

Thomas M. Aaberg, *Atlanta*
Jules Baum, *Boston*
William M. Bourne, *Rochester*
Ronald M. Burde, *New York*
Fred Ederer, *Bethesda*
Frederick T. Fraunfelder, *Portland*
Michael A. Kass, *St. Louis*
Steven G. Kramer, *San Francisco*
Irving H. Leopold, *Irvine*

Robert Machemer, *Durham*
Nancy M. Newman, *San Francisco*
Don H. Nicholson, *Miami*
Edward W. D. Norton, *Miami*
Deborah Pavan-Langston, *Boston*
Allen M. Putterman, *Chicago*
Dennis Robertson, *Rochester*
Merlyn M. Rodrigues, *Baltimore*
Stephen J. Ryan, *Los Angeles*

Jerry A. Shields, *Philadelphia*
M. Bruce Shields, *Durham*
Ronald E. Smith, *Los Angeles*
Bruce E. Spivey, *San Francisco*
Bradley R. Straatsma, *Los Angeles*
H. Stanley Thompson, *Iowa City*
E. Michael Van Buskirk, *Portland*
Gunter K. von Noorden, *Houston*

Published monthly by the OPHTHALMIC PUBLISHING COMPANY
Suite 1415, 435 North Michigan Avenue, Chicago, Illinois 60611

Directors

Edward W. D. Norton, *President*
Bradley R. Straatsma, *Vice President*
Frank W. Newell, *Secretary and Treasurer*

Bruce E. Spivey
Thomas M. Aaberg
Michael A. Kass

PERSPECTIVES

Assessment of Ophthalmic Training Programs

Geoffrey Broocker, M.D., and Thomas M. Aaberg, M.D.

During these times of divided opinion concerning the optimal length of ophthalmology training programs and prompted by an increased knowledge base that must be coordinated with increasingly sophisticated technology, training directors struggle to maintain a proper balance between the training curriculum and the fiscal resources necessary to maintain these programs. Financial obligations to faculty and institutions, decreasing grant support for research involvement, sociopolitical interactions within university faculties and between the academic faculties and private practitioners, and increasing patient care requirements tend to divert departmental energies away from medical education. This phenomenon affects even the strongest programs, placing their educational capabilities at risk. In many instances, faculty members, through perceived or actual necessity, spend increasing time on patient care with decreasing emphasis on teaching activities as their tenure within a program lengthens. Other faculty, struggling to maintain a balance

between clinical and basic research activity, also show decreased availability for resident training. Those faculty members with research programs find annual reductions in support levels routine, rather than the exception. The universities often return none or a bare minimum of the indirect costs to the investigators, so that support of their research is in peril.

Subspecialty fellowship trainees are yet another factor affecting residency training in many programs. When programs are structured properly, fellows enhance resident training by creating a hybridization of differing educational programs. If programs are structured improperly, an adversarial relationship may develop between resident and fellowship trainees.

All of these pressures upon departmental faculty and leadership enhance the need for an accrediting body that can objectively evaluate training programs while maintaining the respect of the ophthalmologic profession, the academic community, and the public they

serve, whose concern is the ultimate professional certification that is granted. Enter the Accreditation Council for Graduate Medical Education.

The activities of the Accreditation Council for Graduate Medical Education as the monitor of ophthalmic education has been described by Trobe and associates¹ and the 1987 Residency Review Committee for Ophthalmology.² These articles presented the purpose, guidelines, and effectiveness of the Residency Review Committee and its parent agency, the Accreditation Council for Graduate Medical Education. The Ophthalmic Residency Review Committee members, several of whom are program directors, have demonstrated awareness of the demands upon training programs while they critically evaluate the degree to which each program meets its responsibilities. Although they strive to ensure that the standards are appropriate and current, the programmatic changes they mandate may take up to three years to implement. Within that time span, a changing consensus may find such new requirements to be unnecessary, inadequate, or inappropriate. The process used by the Residency Review Committee to evaluate a program's compliance with the requirements includes an intensive review of the program description completed by the director. This information, in conjunction with the report of a site visitor (surveyor), is used to make a determination about the program.

The Residency Review Committee's conclusion is expressed in a letter of notification that sets forth the program's accreditation status as well as any citations concerning academic areas that should be addressed. If the Residency Review Committee has taken an adverse action, such as probationary accreditation, the program director is advised of appeal procedures. Program directors, upon receiving the letters of notification, may experience consternation because the language used for a citation on a specific issue may be similar to that received by a different institution, even though one program is given a warning while another is placed on probation. Legal concerns account for the similarity of language despite obvious disparity of program deficiencies or infractions. Nevertheless, the letters of notification do contain an explanation of the program's inadequacies as viewed by the Residency Review Committee.

Maintaining substantial compliance with the approved standards and advancement to higher levels of training excellence are the desired

goals. At times the Residency Review Committee will indicate that a borderline concern could develop into a serious problem. The citation may be directed at the parent institution (for example, to obtain more space) or at the program itself. The Residency Review Committee centers its concerns primarily around faculty, curriculum, training resources (that is, patients, facilities, and the like), and research. Although these concerns are not necessarily placed in order of importance, the committee's interests are focused consistently on the general and special requirements listed in the Directory of Residency Training Programs.³

Since the 1987 update,² 94 programs have been given full or continued approval. Twenty programs have been placed on probation or continued on probation. There has been relative stability in the total number of programs, since new applications equal the number withdrawn, two. Over a 13-year period of considering the appeals of 15 programs placed on probation (usually for two years but may extend to four), 11 cases were sustained and four were reversed (J. T. Boberg, Ph.D., Accreditation Council for Graduate Medical Education, July 1990).

The Accreditation Council for Graduate Medical Education makes every effort not to become involved in issues of manpower. The Federal Trade Commission has made inquiries into certain actions in which such activity was suspected. Although the Residency Review Committee may reduce the number of trainees within certain programs, the overall number of residents maintained a relatively constant balance. It must be recognized that accreditation actions may bring academic program requirements into conflict with community needs. The philosophical question remains unanswered as to whether disadvantaged populations would be better served by residents representative of the population to be served who are trained in a program with excellent resources or by such residents who are trained in a program with limited resources that is more representative of the disadvantaged population. This concern has recently been reflected by the American Medical Association Council on Medical Education's proclamation that there is "the need to define an appropriate balance between education and service."⁴

Standardization of graduate medical education is an eventual necessity, and the Residency Review Committee and the Accreditation Council for Graduate Medical Education cur-

rently provide a foundation to guide programs and thereby serve the public good. It should be reassuring to know that vigilant assessment and supervision of our training programs are being maintained despite legal and political constraints. Having recently provided the Residency Review Committee our own program information and undergone critical survey, we have witnessed the process of viewing our program from another's perspective and conclude that the system indeed works. The dichotomous alternatives are programmatic anarchy or government mandate, and both are unacceptable.

From the Department of Ophthalmology, Emory University School of Medicine, Atlanta, Georgia. This study was supported in part by an unrestricted grant to the Department of Ophthalmology from Research to Prevent Blindness, Inc.

Reprint requests to Geoffrey Broocker, M.D., Depart-

ment of Ophthalmology, Emory University School of Medicine, 1327 Clifton Rd. N.E., Atlanta, GA 30322.

References

1. Trobe, J. D., Fraunfelder, F., Jones, D. B., Kearns, T. P., Kinder, R. S. L., Milder, B., Richards, R., Spencer, W. H., and Weinstein, G. W.: Monitoring ophthalmology graduate education. The Residency Review Committee. *Arch. Ophthalmol.* 100:67, 1982.
2. The Residency Review Committee for Ophthalmology: An update on the accreditation of graduate education in ophthalmology. *Arch. Ophthalmol.* 105:1189, 1987.
3. American Medical Association: The Directory of Graduate Medical Education Programs, 1989-90. Chicago, AMA Publications, 1989, pp. 9 and 71.
4. Council on Medical Education: Principles for graduate medical education. *JAMA* 263:2927, 1990.

LETTERS TO THE JOURNAL

Experimental Nucleus Extraction Through a Capsulorhexis in an Eye With Pseudoexfoliation Syndrome

Ehud I. Assia, M.D.,
Judy P. Hoggatt, M.D.,
and David J. Apple, M.D.

Departments of Ophthalmology (E.I.A., J.P.H., D.J.A.) and Pathology (D.J.A.), Center for Intraocular Lens Research, Storm Eye Institute, Medical University of South Carolina.

Inquiries to David J. Apple, M.D., Department of Ophthalmology, Medical University of South Carolina, 171 Ashley Ave., Charleston, SC 29425.

Maintenance of capsular integrity is necessary to assure long-term fixation and centration of an intraocular lens in the lens capsule. Radial tears of the capsule should be avoided to preserve capsular integrity. Capsulectomy techniques with sharp edges of the capsular margin have a high incidence of radial tears, with 216 of 250 eyes (86%) reported in one series.¹ Capsular fixation was observed in only 76 of the 250 specimens (30%) examined in this study. In recent years, the continuous circular capsulorhexis has been promoted as a technique to reduce anterior capsular tears. This technique is mainly used in conjunction with phacoemulsification. Continuous circular capsulorhexis is seldom used with planned extracapsular cataract extraction because of occasional complications such as zonular rupture, vitreous loss, or unintended intracapsular cataract extraction and lens dislocation to the vitreous. In a study in our laboratory comparing different capsulectomy techniques, however, continuous circular capsulorhexis with manual nucleus extraction resulted in maintenance of the integrity of the capsulectomy margin in all ten cases.² In contrast, other capsulectomy techniques, in conjunction with the standardized nucleus expression technique, resulted in radial tears in all cases. Thus, the experimental setting supported the clinical impression that continuous circular capsulorhexis maintains capsular integrity.

Pseudoexfoliation syndrome is characterized by the presence of fibrillogranular material throughout the anterior segment. Pseudoexfoliative material is often seen covering the zonules and ciliary processes.^{3,4} Patients with pseudoexfoliation syndrome may have spontaneous and intraoperative lens dislocation during extracapsular cataract extraction. Zonular incompetence (more friable zonules) or weakened zonular attachments may contribute to this complication.^{3,4}

One serious complication is the disruption of zonular fibers or tearing of the posterior capsule, which may result in dislocation of the lens nucleus into the vitreous or sunset syndrome of the intraocular lens. Therefore, the surgeon must be careful to avoid excessive zonular stress.

To investigate the application of continuous circular capsulorhexis with planned extracapsular cataract extraction in such eyes, we performed an experimental nucleus expression through a continuous circular capsulorhexis in an eye with pseudoexfoliation obtained post mortem.

An eye obtained post mortem had the pseu-

THE JOURNAL welcomes letters that describe unusual clinical or pathologic findings, experimental results, and new instruments or techniques. The title and the names of all authors appear in the Table of Contents and are retrievable through the Index Medicus and other standard indexing services. Letters must not duplicate data previously published or submitted for publication. Each letter must be accompanied by a signed disclosure statement and copyright transfer agreement published in each issue of THE JOURNAL.

Letters must be typewritten, double-spaced, on 8 1/2 x 11-inch bond paper with 1 1/2-inch margins on all four sides. (See Instructions to Authors.) An original and **two** copies of the typescript and figures must be sent. The letters should not exceed 500 words of text. A maximum of two black-and-white figures may be used; they should be cropped to a width of 3 inches (one column). Color figures cannot be used. References should be limited to five.

Letters may be referred to outside editorial referees for evaluation or may be reviewed by members of the Editorial Board. All letters are published promptly after acceptance. Authors do not receive galley proofs but if the editorial changes are extensive, the corrected typescript is submitted to them for approval.

These instructions markedly limit the opportunity for an extended discussion or review. Therefore, THE JOURNAL does not publish correspondence concerning previously published letters.

doexfoliation syndrome, evidenced by pseudoexfoliative material on the lens capsule and abundant flakes on the zonules and ciliary processes. The cornea and iris were removed to allow clear visualization of the anterior surface of the lens to the equator. With a Castroviejo caliper and methylene blue, the central 6.0-mm zone was marked. A bent 26-gauge needle was used to make the initial cut, and the continuous circular capsulorhexis was completed with Utrata capsule forceps. Nucleus expression was done by injection of balanced salt solution into the vitreous cavity.² This was accomplished by introducing an intravenous catheter into the globe at the 9 o'clock meridian. Balanced salt solution was injected slowly until the nucleus was expressed through the capsular opening (Fig. 1). The cortical material was aspirated with an automated irrigation-aspiration device. The globe was then sectioned in the coronal plane and inspected from its anterior and posterior aspects (Fig. 2).

Inspection of the eye disclosed findings characteristic of pseudoexfoliation, including the presence of exfoliative material on the lens capsule and abundant flakes on the zonules and ciliary processes. Upon introduction of balanced salt solution into the vitreous, the lens began to protrude forward through the central opening. As it began to come up through the capsulotomy, the cortical fibers gave way and



Fig. 1 (Assia, Hoggatt, and Apple). Experimental nucleus extraction in an eye with pseudoexfoliation syndrome. The cornea and the iris were removed, and a 6.0-mm anterior continuous circular capsulorhexis was performed. Balanced salt solution was injected into the vitreous cavity, pushing the entire lens forward. Successful extraction was achieved without tearing the margin of the capsulorhexis.

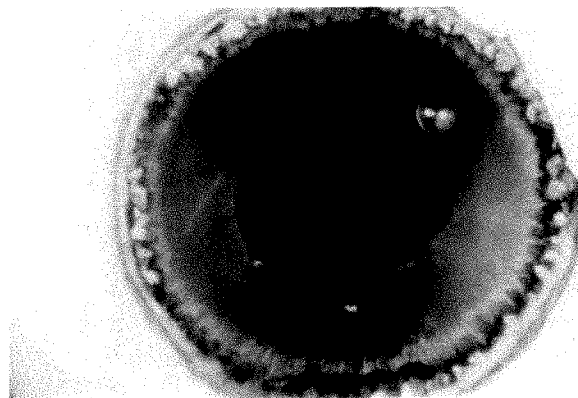


Fig. 2 (Assia, Hoggatt, and Apple). Frontal view of the eye after removal of the nucleus and aspiration of the cortical material. The integrity of the capsulorhexis was maintained, and no evidence of zonular rupture was observed. Note the abundant white and flaky pseudoexfoliative material on the anterior capsule and on the zonular fibers.

opened up in a fashion resembling a flower. As the nucleus was delivered, the capsulotomy was stretched and enlarged. The central core then passed through the cortical material as the superficial layers of the cortex peeled away (Fig. 1). A total of 0.6 ml of balanced salt solution was required to complete the nucleus expression. The diameter of this nucleus core was 7.5 mm, and the thickness was 4.0 mm. In this case, as in other cases in which continuous circular capsulorhexis was performed in our laboratory, the nucleus was delivered successfully without the production of radial tears. There was also no evidence of zonular rupture and no vitreous loss (Fig. 2).

In the clinical setting, manual nucleus expression is usually accomplished by applying external pressure on the globe. We accomplished nucleus expression by the injection of balanced salt solution into the vitreous cavity. This was done to maintain an even distribution of intravitreal pressure as the lens was pushed anteriorly and to eliminate possible bias by the examiner. This expression technique was more stressful to zonules and the anterior capsule as compared to clinical techniques. Nevertheless, even in this eye with pseudoexfoliation, no rupture of the capsulotomy or any rupture of zonules was observed. The calculated largest profile diameter of the nucleus, as viewed in sagittal section, was 19.0 mm. The circumference of a 6.0-mm circular capsulotomy is also 19.0 mm ($\pi \times 6.0$); thus, the nucleus could be expressed without significant stretching of the

capsule. We have shown in another eye with pseudoexfoliation that the continuous circular capsulorhexis was stretched to 1.66 times its original circumference before it ruptured. The zonules, however, were much more friable compared to the normal control eyes.⁵

Clinically, nucleus extraction can be facilitated by hydrodissection and hydroexpression, thus reducing the stress on the zonules. Recently, we showed that this procedure can also be done with viscoelastic materials (viscoextraction). In this modification of hydroextraction, the nucleus is lubricated, and we found the nucleus expression to be more controlled with less stress on the zonules (unpublished data).

Special attention must be given to recognizing zonular dialysis or rupture in eyes with pseudoexfoliation syndrome. Excessive lens movement and phacodonesis may alert the surgeon to the possibility of compensated zonular apparatus.³ Such awareness allows the surgeon to take necessary precautions to prevent subsequent operative complications.

Capsulectomy using the continuous circular capsulorhexis may be applicable to diseased eyes, such as those with pseudoexfoliation syndrome. Careful surgery with minimal stress to zonules is warranted. To this end, the advantages of capsulorhexis, that is, resistance to radial tears and stable fixation of the intraocular lens, can also be achieved in these difficult cases.

References

1. Wasserman, D., Apple, D. J., Castaneda, V. E., Tsai, J. C., Morgan, R., Assia, E. I., Lim, E. S., and Brown, S. J.: Anterior capsular tears and loop fixation of posterior chamber intraocular lenses. *Ophthalmology*. In press.
2. Assia, E. I., Apple, D. J., Barden, A., Tsai, J. C., Castaneda, V. E., and Hoggatt, J. P.: An experimental study comparing various anterior capsulectomy techniques. *Arch. Ophthalmol.* In press.
3. Skuta, G. L., Parrish, R. K., Hodapp, E., Forster, R. K., and Rockwood, E. J.: Zonular dialysis during extracapsular cataract extraction in pseudoexfoliation syndrome. *Arch. Ophthalmol.* 105:632, 1987.
4. Raitta, C., and Setälä, K.: Intraocular lens implantation in exfoliation syndrome and capsular glaucoma. *Acta Ophthalmol.* 64:130, 1986.
5. Assia, E. I., and Apple, D. J.: The relationship between anterior capsular and zonular elasticity. ARVO abstracts. Supplement to *Invest. Ophthalmol. Vis. Sci.* Philadelphia, J. B. Lippincott, 1990, p. 202.

A New Technique for the Administration of Intraoperative Periocular Corticosteroids

Brian C. Joondeph, M.D.

Department of Ophthalmology, Kresge Eye Institute, Wayne State University School of Medicine.

Inquiries to Brian C. Joondeph, M.D., 22151 Moross Rd., Ste. G-30, Detroit, MI 48236.

Periocular corticosteroids are injected routinely after intraocular surgery, usually as an anterior subconjunctival injection. These anterior injections have a beneficial effect on anterior segment inflammation but little or no effect on posterior segment inflammation, including cystoid macular edema. Any periocular injection, including both retrobulbar and peribulbar, carries a small but definite risk of complications, including penetration of the globe.

I developed a new technique for the intraoperative administration of periocular corticosteroids, which permits accurate placement of the medication behind the globe with virtually none of the complications associated with the currently used techniques. The technique has been used only in vitreoretinal surgical procedures but could easily be adapted for use with anterior segment procedures. The injection technique has been described for ocular anesthesia.^{1,2}

Any of the four quadrants can be used, although the temporal quadrants allow easier access to the macular region. At the completion of the surgical procedure, either a Westcott or curved Stevens scissors is used to dissect Tenon's capsule bluntly from the surface of the globe, as performed routinely in scleral buckling or strabismus surgery, unless already performed as part of the surgery (such as in vitreoretinal surgery). A blunt 19-gauge irrigating cannula is attached to a syringe containing the corticosteroid preparation of choice. The cannula is then introduced into the quadrant along the globe and inserted until the hub of the cannula is at the level of the corneoscleral limbus. The tip of the cannula is oriented such that the injection is behind the macula. The corticosteroid preparation is injected slowly, and then the conjunctiva is closed in the usual manner.

The posterior subtenon's corticosteroid is effective in treating cystoid macular edema associated with uveitis.³ My technique makes it virtually impossible to damage the globe, optic nerve, or other periocular tissues and allows

accurate placement of a bolus of medication directly behind the macula where it has its most beneficial effects. The technique is particularly useful in cases in which cystoid macular edema is present preoperatively or is likely to occur postoperatively, including the following: intraocular lens removal or exchange for chronic cystoid macular edema; cataract extraction or pars plana lensectomy and vitrectomy in eyes with uveitis; vitrectomy for endophthalmitis; and cataract extraction or penetrating keratoplasty complicated by vitreous disruption.

References

1. Hansen, E. A., Mein, C. E., and Mazzoli, R.: Ocular anesthesia for cataract surgery. A direct subtenon's approach. *Ophthalmic Surg.* 21:696, 1990.
2. Mein, C. E., and Flynn, H. W., Jr.: Augmentation of local anesthesia during retinal detachment surgery. *Arch. Ophthalmol.* 107:1084, 1989.
3. Smith, R. E., and Nozik, R. A.: Uveitis. A Clinical Approach to Diagnosis and Management. Baltimore, Williams and Wilkins, 1989, pp. 63-68.

Tear Cytology in Conjunctival Melanoma

Jayne S. Weiss, M.D.,
Pascale Perusse, M.D.,
and Frank Reale, M.D.

Division of Ophthalmology, Department of Surgery,
University of Massachusetts Medical Center.

Inquiries to Jayne S. Weiss, M.D., Division of Ophthalmology, Department of Surgery, Rm. S7-834, University of Massachusetts Medical Center, 55 Lake Ave. N., Worcester, MA 01655.

A 67-year-old man had a biopsy-proven conjunctival melanoma involving the bulbar, forniceal, and caruncular regions of the left eye. Areas of brown, crusted secretions were noted on the lower eyelid. We wondered if melanocytic tumor cells were exfoliating into the tears, leaving a pigmented residue on the skin.

To determine if melanoma cells were present in the tears, we used a fine glass capillary tube to collect the tears from either eye. The fluid was passed through a millipore filter to isolate cellular material. After staining with modified Papanicolaou stain, the slides were examined under light microscopy. The specimen from the normal eye was unremarkable. The tear cytology

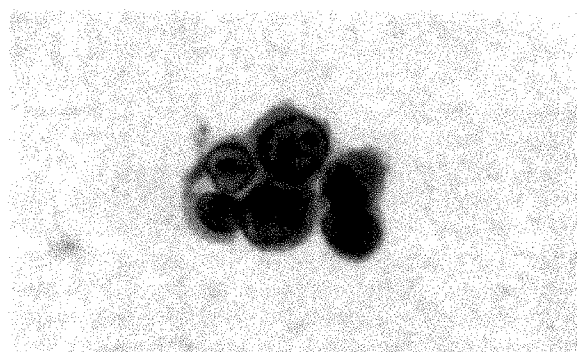


Fig. 1 (Weiss, Perusse, and Reale). Tear specimen from eye with conjunctival melanoma demonstrating malignant pleomorphic cells with macronucleoli and granular cytoplasm (Papanicolaou stain, $\times 400$).

from the left eye, however, demonstrated several clusters of malignant cells with pleomorphic nuclei of varying size containing large round nucleoli (Fig. 1). Because of the similarities between these clusters of cells and the initial biopsy specimen (Fig. 2), these suspicious cells were interpreted as consistent with conjunctival melanoma.

Atypical melanocytes in the tear film may pose a risk of melanoma dissemination to the tear drainage apparatus by direct spread through the tears. The seeding of neoplastic cells through the cerebrospinal fluid circulation has been described.¹ Meningeal melanoma can spread via the subarachnoid space through the cerebrospinal fluid circulation.²

Jakobiec, Folberg, and Iwamoto³ reported the possibility of intraepithelial spread to the lacrimal sac of atypical melanocytes surrounding the lacrimal puncta. Concomitant conjunctival

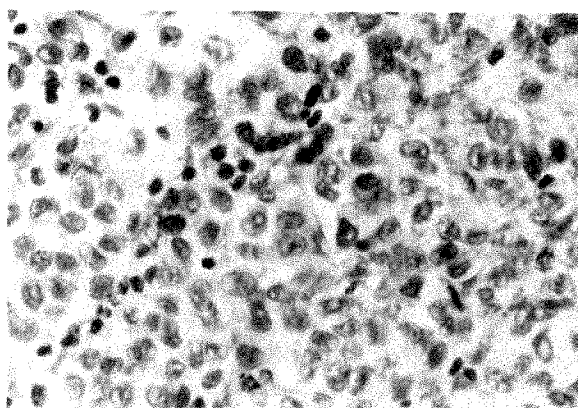


Fig. 2 (Weiss, Perusse, and Reale). High-power view of conjunctival melanoma demonstrating both bland and pleomorphic spindle cells mixed with epithelioid tumor cells containing intracytoplasmic granules (hematoxylin and eosin, $\times 400$).

and lacrimal apparatus melanoma exist. Consequently, to prevent seeding of the melanoma into the lacrimal apparatus, punctal occlusion may be indicated in patients with conjunctival melanoma if tumor exfoliation in the tear film is documented.

References

1. Adams, R. D., and Victor, M.: *Principles of Neurology*, ed. 4. New York, McGraw-Hill, 1989, p. 524.
2. Schmidt, P., Neuen-Jacob, E., Blanke, M., Arendt, G., Weschler, W., and Pfitzer, P.: Primary malignant melanoblastosis of the meninges. Clinical, cytologic and neuropathologic findings and care. *Acta Cytol.* 32:713, 1988.
3. Jakobiec, R. F. A., Folberg, R., and Iwamoto, T.: Clinicopathologic characteristics of premalignant and malignant melanocytic lesions of the conjunctiva. *Ophthalmology* 96:147, 1989.

Epiphora Caused by Blepharoptosis

Herbert J. Glatt, M.D.

Section of Ophthalmology, Department of Surgery, University of Tennessee Medical Center at Knoxville, and Ophthalmology Service, Department of Surgery, East Tennessee Baptist Hospital.

Inquiries to Herbert J. Glatt, M.D., University Eye Surgeons, Ste. 324, 1928 Alcoa Highway, Knoxville, TN 37920.

A 66-year-old man had undergone cataract surgery on the right eye three years before I examined him. The procedure was complicated by prolapse of the nucleus into the vitreous cavity. Because of increased intraocular pres-

sure, a retinal surgeon removed the nucleus six weeks later. A retinal detachment was noted three weeks later, and the patient underwent a scleral buckling procedure. The patient subsequently attained visual acuity of 20/20.

Soon after his ocular operations, the patient noted the simultaneous onset of blepharoptosis and epiphora in the right upper eyelid. Clear, watery tears welled up in his eye and occasionally ran onto his skin near his medial canthus. His vision was blurred by both his blepharoptotic upper eyelid and his watery eye, particularly when reading or playing golf. Lifting his eyelid and wiping his eye cleared his vision.

Examination disclosed blepharoptosis of the right upper eyelid. The vertical palpebral fissure was 4 mm on the right and 6.5 mm on the left. The blepharoptotic right upper eyelid impinged upon the visual axis. Manual elevation of the eyelid subjectively improved his vision. In downgaze, the right eye was completely covered. Levator muscle function on the right was 13 mm. Slit-lamp examination showed apposition of the upper eyelid to the lower eyelid from the medial canthus to slightly lateral to the puncta (Fig. 1). A fine white discharge was noted where the eyelids touched. The cornea was clear and without epithelial abnormalities. The anterior chamber was quiet, with a well-positioned anterior chamber intraocular lens implant. When the upper eyelid was separated from the lower eyelid, there was no apparent punctal stenosis or malposition. Mild laxity of the lower eyelid was noted. After instillation of topical anesthesia, the result of the Schirmer's test was 3 mm at one minute. Probing of the lower canaliculus disclosed no obstruction, and fluid irrigated freely from the lower canaliculus into the nose.



Fig. 1 (Glatt). Left, The blepharoptotic right upper eyelid impinges upon the visual axis. Right, The medial upper eyelid touches the medial lower eyelid from the medial canthus to slightly lateral to the puncta. The puncta are not in contact with the tear film.



Fig. 2 (Glatt). Left, After blepharoptosis surgery, the right upper eyelid no longer impinges upon the visual axis. Right, The medial upper eyelid is now separated from the medial lower eyelid. The puncta are in contact with the tear film.

After instillation of phenylephrine into the right superior conjunctival fornix,¹ the right upper eyelid elevated and cleared the visual axis adequately. The medial upper eyelid became separated from the medial lower eyelid, which allowed contact between the puncta and the tear film. Instillation of phenylephrine on the right also caused the left upper eyelid to drop slightly, which resulted in symmetric upper eyelid heights. The patient preferred to have his more blepharoptotic eyelid raised to match the height of his less blepharoptotic eyelid rather than having bilateral blepharoptosis surgery. On the basis of the phenylephrine test, a Müller's muscle-conjunctival resection blepharoptosis procedure was performed on the right upper eyelid.²

At two weeks postoperatively, the patient noted complete elimination of his epiphora. Six weeks postoperatively, his vision had improved significantly, particularly when reading or playing golf. Examination disclosed a vertical palpebral fissure of 6 mm on each side. The right upper eyelid no longer impinged upon the visual axis. In downgaze, the right vertical palpebral fissure was 1.5 mm. Slit-lamp examination disclosed separation of the medial upper eyelid from the lower eyelid, with the puncta in contact with the tear film (Fig. 2).

Medial canthal crowding (apposition of the upper eyelid to the lower eyelid) caused by upper eyelid blepharoptosis is an uncommon cause of epiphora. Most patients with blepharoptosis do not have this problem. Evaluation of epiphora should include a careful examination of the medial eyelids. If epiphora, blepharoptosis, and medial canthal crowding coexist, blepharoptosis surgery may relieve both the blepharoptosis and the epiphora.

References

1. Glatt, H. J., Fett, D. R., and Putterman, A. M.: Comparison of 2.5% and 10% phenylephrine in the elevation of upper eyelids with ptosis. *Ophthalmic Surg.* 21:173, 1990.
2. Putterman, A. M., and Fett, D. R.: Müller's muscle in the treatment of upper eyelid ptosis. A ten year study. *Ophthalmic Surg.* 17:354, 1986.

Reversible Lower Eyelid Ectropion Associated With Dipivefrin

George B. Bartley, M.D.

Department of Ophthalmology, Mayo Clinic and Mayo Foundation. This study was supported in part by an unrestricted grant from Research to Prevent Blindness, Inc.

Inquiries to George B. Bartley, M.D., Department of Ophthalmology, Mayo Clinic, Rochester, MN 55905.

Topical dipivalyl epinephrine (dipivefrin) is commonly used in the treatment of open-angle glaucoma. Local side effects occur in approxi-



Fig. 1 (Bartley). Left lower eyelid ectropion and eyelid inflammation associated with dipivefrin.

mately 20% of patients and include follicular conjunctivitis, ocular discomfort, eyelid inflammation, cystoid macular edema, and punctate keratopathy.¹⁻⁵ I examined a patient who had lower eyelid ectropion that resolved after dipivefrin eyedrops were discontinued.

A 75-year-old man had ectropion of the left lower eyelid. The eyelid malposition had been noted for approximately one year, and an operation for ectropion (a pentagonal wedge resection) had been performed at another institution six months before my initial examination. Since birth, the patient's right eye had been blind from chorioretinitis and was exotropic. Glaucoma had been diagnosed in the left eye many years previously and had been treated with dipivefrin, one eyedrop daily, for approximately two years. Visual acuity with correction in the left eye was 20/50, consistent with lens opacities. Results of perimetry were normal; gonioscopy allowed visualization of the ciliary body band for 360 degrees; intraocular pressure by applanation tonometry was 21 mm Hg; and the cup/disk ratio for the left eye was 0.7 with a healthy-appearing rim of tissue. The conjunctiva of the left eye was injected mildly; the left upper eyelid was blepharoptotic and slightly inflamed; and the left lower eyelid was thickened, erythematous, and ectropic with contracture of the anterior lamella (Fig. 1).

The dipivefrin eyedrop was discontinued. Within three weeks, the eyelid inflammation had nearly resolved, and the ectropion had improved markedly (Fig. 2). Diurnal tonometry was performed; the highest intraocular pressure in the left eye was 20 mm Hg. Results of tonography were normal. No antiglaucoma treatment other than observation was thought necessary, and during a follow-up period of two years there has been no progression of the size of the optic cup. The left lower eyelid has remained in normal position.

Dipivefrin hydrochloride contains dipivefrin, mannitol, sodium metabisulfite, disodium edetate, and benzalkonium chloride.³ Although

benzalkonium may cause contact dermatitis, a recent study documented that dipivefrin is responsible for the blepharoconjunctivitis that is frequently associated with this drug.³ The contact hypersensitivity is rarely sufficiently severe to cause eyelid ectropion, as in my patient. A trial of discontinuation of dipivefrin should be considered before surgical intervention for the eyelid malposition is performed.

References

1. Liesegang, T. J.: Bulbar conjunctival follicles associated with dipivefrin therapy. *Ophthalmology* 92:228, 1985.
2. Wandel, T., and Spinak, M.: Toxicity of dipivalyl epinephrine. *Ophthalmology* 88:259, 1981.
3. Petersen, P. E., Evans, R. B., Johnstone, M. A., and Henderson, W. R.: Evaluation of ocular hypersensitivity to dipivalyl epinephrine by component eye-drop testing. *J. Allergy Clin. Immunol.* 85:954, 1990.
4. Mehelas, T. J., Kollarits, C. R., and Martin, W. G.: Cystoid macular edema presumably induced by dipivefrin hydrochloride (Propine). *Am. J. Ophthalmol.* 94:682, 1982.
5. Boerner, C. F.: Total punctate keratopathy due to dipivefrin. *Arch. Ophthalmol.* 106:171, 1988.

Contrast Sensitivity as an Early Indicator of Acute Mountain Sickness

Jean-Philippe Nordmann, M.D.,
Jean-Philippe Roncin, M.D.,
Philippe Denis, M.D.,
Jean-Pierre Blein, M.D.,
and Henry Saraux, M.D.

Department of Ophthalmology, Hôpital Saint-Antoine. This study was presented in part as a poster at the Association for Research in Vision and Ophthalmology Annual Meeting in Sarasota, Florida, April 28, 1991.

Inquiries to Jean-Philippe Nordmann, M.D., Department of Ophthalmology, Hôpital Saint-Antoine, 184, Faubourg Saint-Antoine, F-75012 Paris, France.

Acute mountain sickness is a debilitating illness of travelers who rapidly ascend to altitudes above 3,000 m. The disease is characterized by headache, lassitude, anorexia, nausea, and vomiting. Visual function is likely to be impaired by this disease, but simple tests, such as visual acuity, are usually not included in the



Fig. 2 (Bartley). Within three weeks of discontinuation of dipivefrin, the ectropion and eyelid inflammation improved markedly.

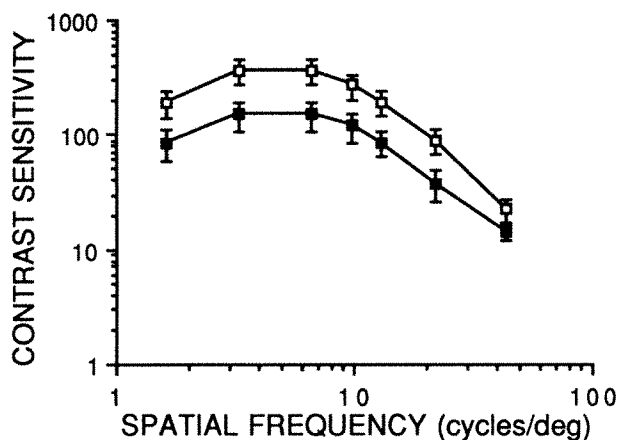


Fig. 1 (Nordmann and associates). Mean contrast sensitivity for the 12 subjects as measured at sea level (open squares) and the day after arrival at 5,400 m (filled squares). Error bars show \pm standard errors.

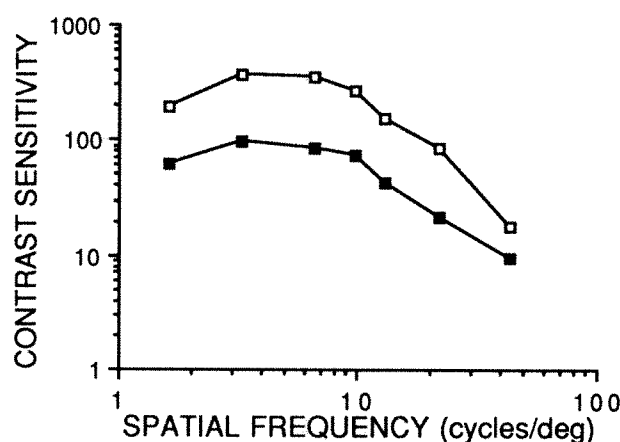


Fig. 2 (Nordmann and associates). Contrast sensitivity for one patient who had acute mountain sickness (filled squares). Contrast sensitivity did not improve spontaneously after three days. Twelve hours after administration of prednisolone, thresholds were back to sea level values (open squares).

evaluation of this illness because they are not sensitive enough to detect early signs of hypoxia and alkalosis caused by the low level of oxygen pressure in high altitudes.¹ To find an early indicator of these disturbances, we tested contrast sensitivity at high altitude.

Twelve healthy subjects, ranging in age from 29 to 41 years, were tested in the Himalayas at a base camp of 5,400 m. The climbers reached this camp after a four-day trek originating at 2,000 m. Tests were performed twice a day during the first three days after arrival at base camp. Additionally, contrast sensitivity was also tested when the subjects returned to the base camp, after trekking on peaks of up to 8,000 m. Experiments were conducted in a tent. Screen luminance of 80 cd/m² as well as background luminance of 10 cd/m² were kept constant throughout the sessions. Contrast sensitivity measurements were taken binocularly at seven spatial frequencies, ranging from 1.5 to 40.0 cycles per degree, using gratings generated on a video screen under computer control. Subjects were seated 3 m from the screen and asked to detect the orientation of static sinusoidal gratings with a forced-choice method. After four reversals, contrast thresholds corresponding to 75% correct answers were recorded. Additionally, subjects underwent visual acuity and fundus examination performed with a direct ophthalmoscope.

A decrease of contrast sensitivity was seen constantly ($P < .01$) in all subjects the day after their arrival at the base camp of 5,400 m. This impairment was for the most part evident in

low and medium spatial frequencies ranging from -2.0 to -4.9 dB less than sea level values as measured in France before the expedition (Fig. 1). Despite contrast sensitivity loss, no subject perceived visual impairment or had decreased visual acuity. Contrast sensitivity returned to normal after 36 hours and remained so for as long as the subjects stayed at the same altitude. No retinal hemorrhage was detected in the 12 subjects.

Contrast sensitivity tested at the base camp did not change after treks to higher altitude, except in one case. One subject had sudden fatigue and headache after a short ascent of 400 m from the base camp, which was an acute mountain sickness crisis. This subject went back immediately to the base camp where contrast sensitivity was tested. A dramatic decrease of contrast sensitivity was recorded without change of visual acuity (Fig. 2). Contrast sensitivity loss reached -6.0 dB at medium spatial frequencies. Contrast sensitivity was then tested every 12 hours and showed no improvement after three days. Because signs of mountain sickness did not disappear spontaneously, 10 mg of prednisolone was administered. The drug relieved the general symptoms and restored contrast sensitivity to sea level values after 12 hours.

Early swelling of the brain has been suggested as the cause of acute mountain sickness,² and corticosteroids have been shown to relieve symptoms in patients with mountain sickness associated with cerebral edema.³ In our subject

who had an acute crisis, the efficiency of corticosteroids in correcting contrast sensitivity loss supports the role of edema as a factor in the pathogenesis of the visual symptoms.

Contrast sensitivity impairment was an early sign of cerebral or retinal disturbances caused by altitude hypoxia. This simple test could be useful in monitoring acclimatization to high altitude and in patients with hypoxia of another origin. Hence, contrast sensitivity could give a quantitative evaluation of brain and retinal disturbances caused by hypoxia.

References

1. Sampson, J. B., Cymerman, A., Burse, R. L., Maher, J. T., and Rock, P. B.: Procedures for the measurement of acute mountain sickness. *Aviat. Space Environ. Med.* 54:1063, 1983.
2. Hackett, P. H., Rennie, D., Grover, R. F., and Reeves, J. T.: Acute mountain sickness and the edemas of high altitude. A common pathogenesis? *Respir. Physiol.* 46:383, 1981.
3. Levine, B. D., Yoshimura, K., Kobayashi, T., Fukushima, M., Shibamoto, T., and Ueda, G.: Dexamethasone in the treatment of acute mountain sickness. *N. Engl. J. Med.* 321:1707, 1989.

Bilateral Endogenous Endophthalmitis in a Patient With Diabetes and Renal Papillary Necrosis

Richard H. Havunjian, M.D.,
Robert A. Goldberg, M.D.,
and Robert S. Hepler, M.D.

Department of Ophthalmology, Jules Stein Eye Institute, UCLA School of Medicine.

Inquiries to Robert A. Goldberg, M.D., Jules Stein Eye Institute, 100 Stein Plaza, UCLA School of Medicine, Los Angeles, CA 90024.

Endogenous endophthalmitis is a rare but devastating complication in patients with septicemia. *Klebsiella pneumoniae* has been implicated as the etiologic organism in two series of endogenous endophthalmitis, and an association with liver abscess has been described.^{1,2} We treated a patient with bilateral endogenous

panophthalmitis caused by *K. pneumoniae* who had diabetes and renal papillary necrosis.

A 67-year-old woman with a 20-year history of insulin-dependent diabetes was referred to our institution with a diagnosis of mucormycosis. The patient noted floaters and flashes in her left eye approximately seven days before the initial examination, and she lost light perception over the ensuing two days. Subsequently, she developed similar symptoms in her right eye with loss of vision. The patient was admitted to another hospital where blood and urine cultures were obtained and intravenous cefazolin and amphotericin B were started. The next day she was transferred to our institution with a presumptive diagnosis of mucormycosis.

On initial examination, the patient had visual acuity of no light perception in each eye. Tense proptosis, periorbital edema, and erythema were accompanied by severe conjunctival injection bilaterally. Extraocular muscle ductions were significantly limited. Pupils were fixed and mid-dilated. Both corneas were edematous with folds in Descemet's membranes. Anterior chambers were shallow with severe cell and flare. Fundi could not be visualized with indirect ophthalmoscopy. Orbital ultrasound disclosed bilateral organizing vitreous debris, posterior scleral thickening, and choroidal detachments (Fig. 1). On a computed tomographic scan the sinuses were clear, but there was irregular shaggy thickening and enhancement of both sclerae and periocular soft tissues (Fig. 2). A magnetic resonance imaging study of the orbits showed clear orbital apices and clear

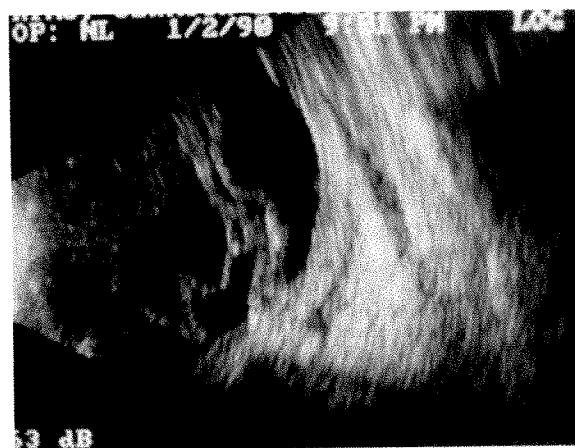


Fig. 1 (Havunjian, Goldberg, and Hepler). Orbital ultrasound showing dense vitreous opacification with membrane formation, posterior scleritis, and diffuse orbital widening with infiltrates.

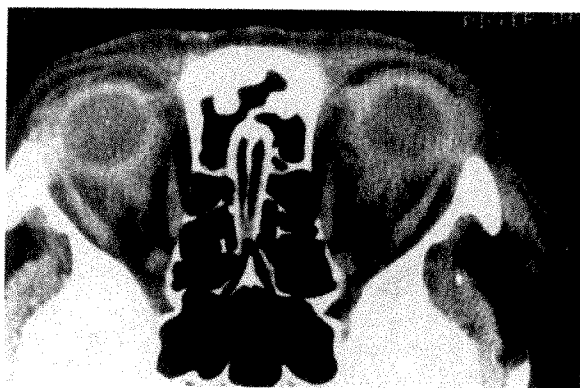


Fig. 2 (Havunjian, Goldberg, and Hepler). Orbital computed tomographic scan showing posterior scleral thickening, anterior orbital inflammation, and enhancement of the muscle tendons and periocular soft tissues. Note that the sinuses are clear.

cavernous sinuses bilaterally. Cerebrospinal fluid, blood, and urine cultures were obtained, and laboratory testing for collagen vascular diseases was done. Vitreous and adnexal (posterior Tenon's capsule and lateral rectus muscle) biopsy was carried out. The initial Gram stain of the vitreous aspirate disclosed gram-negative bacteria. A presumptive diagnosis of endogenous bilateral panophthalmitis was made, and a regimen of intravenous clavulanate potassium and ticarcillin disodium and amphotericin B was begun.

Subsequently, vitreous aspirate and urine cultures from the other hospital yielded *K. pneumoniae* organisms. All other cultures remained negative. Extensive search for the source of infection included gallbladder sonogram and hepato-iminodiacetic acid scan, barium enema, echocardiogram, chest, abdominal, and pelvic computed tomographic scans, and multiple chest, abdominal, and dental x-rays. Findings included filling defects in the left renal pelvis, left ureteral dilation, and multiple nodules in both lung bases. After the repeat vitreous biopsy on the seventh hospital day was negative for bacteria and fungi, amphotericin B was discontinued and ceftizoxime sodium was substituted for clavulanate potassium and ticarcillin disodium. Over the next three weeks, the patient's periorbital edema gradually subsided, and extraocular muscle function partially returned. She continued, however, to have visual acuity of no light perception in both eyes. A subsequent outpatient intravenous pyelogram disclosed extensive left renal papillary necrosis.

Endogenous endophthalmitis with enteric gram-negative bacilli is a devastating ocular infection, which usually results in blindness or loss of the eye.³ The course can be fulminant, as in our case in which panophthalmitis and secondary orbital inflammation simulated mucormycosis. Chiu, Lin, and Liaw¹ described the occurrence of *K. pneumoniae* endophthalmitis in three patients in a consecutive series of 180 patients with liver abscess. Extensive medical examination in our patient disclosed severe renal papillary necrosis associated with diabetes; however, no evidence of involvement of the hepatobiliary tree was present. Renal outflow obstruction resulted in urinary infection and brief septicemia, with bacteria seeding to both globes in a relatively short period of time, as well as to both lungs. Liu, Cheng, and Lin² described four of seven patients with endophthalmitis associated with liver abscess who had visual symptoms as an initial manifestation of the abscess. This suggests that the infection tends to spread to the eye relatively early in the course of septicemia. Thus, endogenous endophthalmitis should be considered in the differential diagnosis of patients with diabetes and acutely decreased vision.

References

1. Chiu, C. T., Lin, D. Y., and Liaw, Y. F.: Metastatic septic endophthalmitis in pyogenic liver abscess. *J. Clin. Gastroenterol.* 10:524, 1988.
2. Liu, Y. C., Cheng, D. L., and Lin, C. L.: *Klebsiella pneumoniae* liver abscess associated with septic endophthalmitis. *Arch. Intern. Med.* 146:1913, 1985.
3. Greenwald, M. J., Wohl, L. A., and Sell, C. H.: Metastatic bacterial endophthalmitis. A contemporary reappraisal. *Surv. Ophthalmol.* 31:81, 1986.

Clostridium perfringens Endophthalmitis

Stephen B. Wiles, M.D.,
and Carl H. Ide, M.D.

Mason Institute of Ophthalmology, University of Missouri-Columbia.

Inquiries to Stephen B. Wiles, M.D., Mason Institute of Ophthalmology, University of Missouri-Columbia, Columbia, MO 65212.

A 14-year-old boy was referred for examination five hours after injuring his left eye while

constructing a shelter for farm animals. He immediately removed the nail that had pierced his eye. The right eye had visual acuity of 20/20 and was physically unremarkable. The left eye had visual acuity of counting fingers at 4 inches. The cornea was perforated inferonasally. Fibrin, lens material, and blood were observed in the shallow anterior chamber. Iris plugged the wound, and the lens was cataractous. There was no intraocular foreign body visible on physical examination or orbital computed tomography. There was no afferent pupillary defect, and motility was normal. Eight hours after the injury, the corneal laceration was repaired, and extracapsular cataract extraction was performed. The posterior capsule was not removed since it appeared to be intact. Intraoperatively, a posterior retinal hemorrhage was observed, but the vitreous was clear. Intravitreal antibiotics were not given. Subconjunctival gentamicin sulfate and cefazolin were injected, and a regimen of intravenous gentamicin sulfate and penicillin and topical gentamicin sulfate was begun. Postoperatively, visual acuity was bare light perception.

A left afferent pupillary defect was noted on the first postoperative day. A dense corneal infiltrate bordered the laceration (Figure). B-scan ultrasonography disclosed mild vitreous debris. Topical fortified gentamicin sulfate and cefazolin were administered hourly. The culture of the lens material was negative at 24 hours, but growth of *Clostridium perfringens* was detected at 48 hours. A repeat sonogram suggested either a heightened vitreal inflammatory response or endophthalmitis. A secondary posterior capsulotomy and pars plana vitrectomy were performed to remove any remaining *Clostridium* organisms and exotoxins. The infusion was supplemented with 0.1 ml of gentamicin sulfate (40 mg/ml) and 0.03 ml of clindamycin (120 mg/ml) per 500 ml of balanced salt solution. At 72 hours the organism was found to be sensitive to chloramphenicol, cefoxitin, and metronidazole but resistant to clindamycin. Six days later, the patient was discharged with visual acuity of hand motions. Eighteen months after the injury, best-corrected visual acuity was 20/40. A left afferent pupillary defect persisted.

Clostridium perfringens endophthalmitis usually occurs after penetrating trauma, with or without a retained intraocular foreign body.¹ Duke-Elder and MacFaul² outlined six distinctive clinical signs associated with gas gangrene panophthalmitis that usually precede loss of



Figure (Wiles and Ide). Corneal edema and infiltration after repair of the laceration and lensectomy. A fibrinoid anterior chamber blurs iris details. Visual acuity is light perception.

the globe within 24 hours. Leavelle¹ reviewed 58 cases of clostridial panophthalmitis, and all globes were either eviscerated or enucleated. Crock and associates³ described a patient with a retained globe and useful visual acuity (20/60) after ocular infection with *C. perfringens*. This patient had bilateral posttraumatic involvement that led to enucleation of the right eye but preservation of the left eye. An aqueous sample from the left eye produced growth of *C. perfringens*. There was no lenticular or vitreal infection, and the patient did well after anterior chamber irrigation.

We attribute the favorable outcome in our patient to early lensectomy and subsequent vitrectomy that apparently removed the nidus of infection as well as exotoxins before irreversible toxicity could occur. An afferent pupillary defect and loss of visual acuity to light perception after the injury suggested initial exotoxin toxicity.

Penicillin is the treatment of choice for clostridial infections; however, systemic antibiotic treatment of clostridial endophthalmitis has not been successful.¹ Although prompt inter-

vention appears to be crucial for survival of the globe in posttraumatic *C. perfringens* endophthalmitis, the diagnosis and treatment of this infection before exotoxins destroy ocular tissue is difficult since this occurs rapidly.

References

1. Leavelle, R.: Gas gangrene panophthalmitis. Arch. Ophthalmol. 53:634, 1955.
 2. Duke-Elder, S., and MacFaul, P. A.: Injuries. Mechanical Injuries. In Duke-Elder, S. (ed.): System of Ophthalmology, vol. 14, pt. 1. London, Henry Kimpton, 1972, pp. 405-410.
 3. Crock, G., Heriot, W. J., Janakiraman, P., and Winer, J.: Gas gangrene of the eyes and orbits. Br. J. Ophthalmol. 69:143, 1985.
-

Correspondence

Correspondence concerning recent articles or other material published in THE JOURNAL should be submitted within six weeks of publication. Correspondence must be typed double-spaced, on 8½ × 11-inch bond paper with 1½-inch margins on all four sides and should be no more than two typewritten pages in length.

Every effort will be made to resolve controversies between the correspondents and the authors of the article before publication.

Delayed-Onset Pseudophakic Endophthalmitis

EDITOR:

In the article, "Delayed-onset pseudophakic endophthalmitis," by G. M. Fox, B. C. Joondeph, H. W. Flynn, Jr., S. C. Pflugfelder, and T. J. Roussel (Am. J. Ophthalmol. 111:163, February 1991), ten of the 19 patients had recurrence of culture-positive endophthalmitis after vitrectomy with injection of subconjunctival and intraocular antibiotics.

Three years ago, we treated a patient with pseudophakic *Propionibacterium acnes* endophthalmitis occurring 18 months after cataract surgery. He underwent a total posterior vitrectomy, removal of a large plaque on the posterior capsule, injection of intraocular vancomycin hydrochloride (1 mg), and subconjunctival injection of vancomycin hydrochloride (25 mg).

No intravenous or prolonged topical antibiotic therapy was used. The inflammation initially improved but then gradually recurred. Two months after the initial operation, the patient was once again found to have endophthalmitis with a positive culture. He was then admitted to the hospital for one week of intravenous vancomycin hydrochloride therapy and treatment with topical vancomycin hydrochloride (50 mg/ml) every one to two hours for two weeks. The inflammation gradually subsided with prednisolone eyedrops four times daily, and within three months all medications were discontinued with no residual inflammation.

Since our experience with this patient, we have treated three other patients with pseudophakic culture-positive *P. acnes* endophthalmitis. All patients underwent vitrectomy with removal of the central posterior capsule, injection of intraocular vancomycin hydrochloride, and a regimen of five to seven days of intravenous vancomycin hydrochloride and frequent topical vancomycin hydrochloride eyedrops for two weeks. The intravenous vancomycin hydrochloride was initially given to each patient at a dosage of 1 g every 12 hours. Peak and trough levels were obtained throughout the course of therapy, and the intravenous doses were adjusted accordingly to maintain therapeutic blood levels at all times. No cases of renal toxicity developed.

The intraocular inflammation resolved totally in all of the patients within three months of therapy using topical prednisolone, and the patients are currently not taking any antiinflammatory medications.

We believe that systemic and topical vancomycin hydrochloride therapy may be necessary to eradicate infection totally by organisms such as *P. acnes*, and this may help to explain why so many of the patients described by Fox and associates had recurrence of their endophthalmitis.

MARK H. HAIMANN, M.D.
HAROLD WEISS, M.D.
JOEL A. MILLER, M.D.
Southfield, Michigan

Reply

EDITOR:

We read with interest the cases of *Propionibacterium acnes* endophthalmitis reported by Drs. Haimann, Weiss, and Miller. We share

their concern that recurrence of infection despite an apparent initial cure is a major problem in those cases of delayed-onset endophthalmitis caused by *P. acnes*. Of five patients in our series with *P. acnes* infection treated initially with injection of intraocular antibiotics without vitrectomy, recurrent infection occurred in four patients, which was subsequently cured by vitrectomy and intraocular antibiotics. Of the seven patients treated with initial vitrectomy and intraocular antibiotics, recurrent inflammation occurred in three patients. These episodes of recurrent inflammation often occurred months after initial treatment. Therefore, long-term follow-up of these cases is mandatory in evaluating any treatment modality for this problem. Drs. Haimann, Weiss, and Miller do not provide the length of follow-up of three of the patients they have treated for *P. acnes* endophthalmitis.

Although we recommend vancomycin hydrochloride as an intraocular antibiotic for treating delayed-onset endophthalmitis, this potentially toxic medication may not be necessarily the only or best choice for systemic therapy in confirmed cases of *P. acnes* endophthalmitis. *Propionibacterium acnes* is often sensitive to numerous antibiotics, including the less toxic third-generation cephalosporins.¹ Good intraocular levels after systemic therapy with cephalosporins have been demonstrated in animal models.² If systemic therapy is to be considered after confirmation of *P. acnes* infection by culture of intraocular specimens, a cephalosporin may be a more logical choice. Because we did not use prolonged intravenous medications in a significant number of our patients with delayed-onset endophthalmitis, we are unable to draw any conclusions about the effectiveness of this form of treatment in reducing the number of recurrences in these cases.

Further animal research studies on intraocular antibiotic penetration are needed to determine the most appropriate systemic treatment for these and other categories of intraocular infections.

GREGORY M. FOX, M.D.
BRIAN C. JOONDEPH, M.D.
HARRY W. FLYNN, JR., M.D.
STEPHEN C. PFLUGFELDER, M.D.
THOMAS J. ROUSSEL, M.D.
Miami, Florida

References

1. Wang, W. L. L., Everett, E. D., Johnson, M., and Dean, E.: Susceptibility of *Propionibacterium acnes* to seventeen antibiotics. *Antimicrob. Agents Chemother.* 11:171, 1977.
2. Martin, D. F., Ficker, L. A., Aguilar, H. A., Gardner, S. K., Wilson, L. A., and Meredith, T. A.: Vitreous cefazolin levels after intravenous injection. Effects of inflammation, repeated antibiotic doses, and surgery. *Arch. Ophthalmol.* 108:411, 1990.

Increased Intraocular Pressure in Severely Burned Patients

EDITOR:

In the article, "Increased intraocular pressure in severely burned patients," by L. S. Evans (*Am. J. Ophthalmol.* 111:56, January 1991), three patients were described with increased intraocular pressure secondary to increased orbital pressure and congestion after severe body and facial burns. Treatment of these three patients included a lateral canthotomy but not a cantholysis (division of the attachment of the lateral canthal tendon to the lateral orbital rim). All three patients had a significant decrease in intraocular pressure, but "none of the eyes had normal intraocular pressure after canthotomy." The author attributes this to "incompleteness of the canthotomy and residual high orbital pressure."

Increased intraorbital and secondary increased intraocular pressure can occur from any increase in the volume of the soft tissues within the bony confines of the orbit. Pressure increases in the orbit because the eyelid tarsal plates with firm attachment to the posterior lacrimal crest and the lateral orbital rim prevent anterior expansion of the orbital contents. An increase in orbital soft tissue volume may be secondary to fluid shifts from the intravascular to the extravascular space in burned patients, orbital hemorrhage after any type of eyelid or orbital surgery, purulent material in patients with orbital infection with or without abscess formation, or orbital air after medial orbital wall or orbital floor fracture. If vision is compromised because of increased intraocular or intraorbital pressure, release of the tarsal ligamentous sling of the upper and lower eyelids should be considered. A lateral can-

thotomy only will allow a limited amount of anterior orbital decompression since the tarsal ligamentous sling remains intact, which prevents anterior orbital decompression. Substantial anterior decompression can only be achieved by lysis of the superior and inferior limbs of the lateral canthal tendon at their attachment to the lateral orbital rim.¹ This allows anterior displacement of the globe and adjacent orbital soft tissues, which decreases orbital and ocular pressure.

RUSSELL W. NEUHAUS, M.D.
Austin, Texas

Reference

1. Neuhaus, R. W.: Complications of Blepharoplasty. Focal Points 1990. Clinical Modules for Ophthalmologists, vol. 8, module 3. San Francisco, American Academy of Ophthalmology, 1990, pp. 1-7.

Reply

EDITOR:

Dr. Neuhaus emphasizes that cantholysis provides a more complete orbital decompression than lateral canthotomy. If a lateral canthotomy is to be done, it should be carried to the orbital rim and the skin incised beyond the rim to achieve maximum effect. In two of my patients, I observed marked anterior displacement of the globe immediately after lateral canthotomy was performed. Lateral canthotomy usually heals well without further surgical procedure; however, if cantholysis were done, it would probably have been necessary to reattach the canthal tendons later to correct a rounding deformity of the lateral canthus. One might consider performing lateral canthotomy first, to be followed by cantholysis if intraocular pressure remains unacceptably increased. If an eyelid has sustained a full-thickness (third-degree) skin burn, a scar with contracture deformity is likely to occur, and this may lead to an ectropion with exposure of the globe. In this case, I am concerned that cantholysis could facilitate a medial contracture deformity and exacerbate problems with exposure and reattachment of the tendon.

LAWRENCE S. EVANS, M.D.
Maywood, Illinois

Surgical Management of Oculomotor Nerve Palsy

EDITOR:

In the article, "Surgical management of oculomotor nerve palsy," by I. Gottlob, R. A. Catalano, and R. D. Reinecke (*Am. J. Ophthalmol.* 111:71, January 1991), the authors describe their technique of anterior transposition of the ipsilateral superior oblique tendon (Scott procedure). We agree that differences in surgical technique may have accounted for the frequent occurrence of hypertropia and paradoxical ocular movements in our previously reported cases.¹ Their assertion that the Scott procedure is effective in restoring or maintaining primary position alignment is speculative, however, since it was always accompanied by extensive horizontal rectus muscle surgery. We continue to believe that horizontal rectus muscle surgery alone can provide satisfactory long-term results in most patients with oculomotor nerve palsy and have yet to see convincing evidence that superior oblique muscle transposition is either necessary or helpful.

RICHARD A. SAUNDERS, M.D.
Charleston, South Carolina
GARY L. ROGERS, M.D.
Columbus, Ohio

Reference

1. Saunders, R. A., and Rogers, G. L.: Superior oblique transposition for third nerve palsy. *Ophthalmology* 89:310, 1982.

Reply

EDITOR:

We concur with Drs. Saunders and Rogers that changing surgery certainly may make the results better, but our data do substantiate our claim that the Scott procedure (with adequate horizontal muscle surgery) is effective in restoring or maintaining the primary position alignment with long follow-up periods. We would further note that our clinical results before the use of the superior oblique muscle as a tonic adduction force were poor. Those poor results were, after several years, that the operated on eyes would drift down and out to a position close to the original misalignment.

Those of us who have followed up cases for long periods of time, particularly in clinics such as the Massachusetts Eye & Ear Infirmary where numerous surgeons operated on eyes with oculomotor palsy with many years of poor results before the transplantation of the tendon of the superior oblique muscle, realize that the maintenance of the initial surgical results is difficult in these cases. It was not until transposition of the superior oblique tendon became an accepted procedure that the eyes remained straight for long periods of time.¹ Further, the original transplantation out of the trochlea was a difficult procedure, and we have been pleased with the Scott procedure, which is simpler in maintaining the mild amount of tension necessary for alignment. Those ophthalmologists who fail to take into account the continued shortening of muscles that are unopposed realize the importance of this consideration.

I hope that readers will not be unduly influenced by speculation that only horizontal surgery without an opposing chronic tension source will maintain alignment. If, however, Drs. Saunders and Rogers have long-term data on good results, they should publish it.

IRENE GOTTLOB, M.D.

ROBERT D. REINECKE, M.D.

Philadelphia, Pennsylvania

ROBERT A. CATALANO, M.D.

Albany, New York

Reference

1. Saunders, R. A., and Rogers, G. L.: Superior oblique transposition for third nerve palsy. *Ophthalmology* 89:310, 1982.
-

BOOK REVIEWS

Edited by H. Stanley Thompson, M.D.

Books Received

Orthoptic Assessment and Management. By David Stidwill. St. Louis, Mosby-Year Book, 1990. 182 pages, index, illustrated. \$59.95

This text is directed toward optometric final examinations in the United Kingdom. It includes a thorough review of exercises for abnormalities of convergence and accommodation, but there is too much emphasis on anomalous retinal correspondence and how to make the diagnosis. Anomalous retinal correspondence is an uncommon condition that is seldom troublesome. Most readers need help in understanding the theoretic basis of anomalous retinal correspondence, and this book does not provide it.

Wally, The Scholarly Walrus. By Lee Hill. New York, Vantage Press, 1990. 23 pages, illustrated. \$6.95

Children's books, such as this one, help kids through almost any imaginable emotional crisis. A school-age walrus needs spectacles, so his mom takes him to the eye doctor. He worries

about his self image until a sensitive girl walrus tells him he looks "distinguished!" Twelve charming pen and ink drawings by Wally Littman are included. In pamphlet form, this might be worth giving out with new prescriptions for spectacles.

The Book List

Advances in Ophthalmic Plastic and Reconstructive Surgery. By Stephen L. Bosniak and Byron C. Smith. Philadelphia, Pergamon Press, 1990. 288 pages, index, illustrated. \$82.50

Focal Points 1990. Clinical Modules For Ophthalmologists. San Francisco, American Academy of Ophthalmology, 1990. 12 sections, index. \$85 members, \$110 nonmembers

How to Write and Publish Papers in the Medical Sciences, ed. 2. Edited by Edward J. Huth. Baltimore, Williams & Wilkins, 1990. 252 pages, index. \$29.95

Scanning Laser Ophthalmology and Tomography. By J. E. Nasemann and R. O. W. Burk. Lombard, IL, Quintessence Publishing, 1991. 271 pages, index, illustrated. \$140

OPHTHALMIC MINIATURE

The only father I knew was a big painting that hung in the main hall. He was a large, unsmiling man, unhappy to be so still on the wall. His restless eyes followed me around the house. Even from my room at the end of the hall, I could see my father's watching eyes. Popo said he watched me for any signs of disrespect. So sometimes, when I had thrown pebbles at other children at school, or had lost a book through carelessness, I would quickly walk by my father with a know-nothing look and hide in a corner of my room where he could not see my face.

Amy Tan, *The Joy Luck Club*
New York, G. P. Putnam's Sons, 1989, p. 43

Obituary

RONALD G. MICHELS

1943-1991

On Jan. 15, 1991, ophthalmology and the subspecialty of vitreoretinal diseases lost a great leader, teacher, and physician, Ron Michels.

Ron grew up in the small town of Henderson, North Carolina. He attended the University of North Carolina, where he was an outstanding student and a member of the Tar Heel golf team. In his characteristically generous manner, Ron freely gave golf tips to his friends throughout his life; many of us have enjoyed his recounting of his efforts to school us over the years. He remained at Chapel Hill for medical school, where he worked with Sam McPherson, who urged Ron to consider his alma mater, Wilmer Ophthalmological Institute, for residency. In 1968, Ron went to Baltimore for an internship in medicine at Johns Hopkins, and he entered his ophthalmology residency at Wilmer one year later.

My friendship and respect for Ron commenced on July 1, 1969, my first day as chief resident and his first day as a resident at the Wilmer Institute. This chief resident/first-year resident relationship provided the opportunity to form close friendships, because the approach at Wilmer was to employ the Socratic method and to involve the residents actively in case discussions. I will never forget that first day when, in my position of leader, I asked for a presentation of the first patient for the academic year, a patient with sarcoidosis. I had not really known any of the first-year residents before these rounds, and I randomly chose Ron to discuss the disease process of sarcoidosis. Thirty minutes later, he was still speaking! His discussion was extraordinarily well organized; there was no hesitation, no repetition, and no "um's" or "ah's." Indeed, any visiting professor would have been proud to have given such a thorough presentation as was delivered by this young physician on his first day as an ophthalmology resident. I knew immediately that Ron Michels had the makings of a superstar in ophthalmology. During the remainder of his residency, Ron made major contributions to the success of the resident teaching program and to the highest standard of care in the Wilmer Clinic. His great knowledge and organization, combined with an incredible work ethic, made him a stalwart upon whom all of the other



Ronald G. Michels

1943-1991

residents and I came to rely. As residents and young faculty at Wilmer, Ed Maumenee was our professor and role model. One of the best things the "Prof" ever did for me was to select Ron as a first-year resident for our group.

After his residency, Ron moved on to Bascom Palmer as a retina-vitreous fellow. This was a particularly exciting time for those interested in retinal diseases, and Ron recalled that he was fortunate to work under the guidance of Ed Norton and the rest of the outstanding group in Miami, including Don Gass, Victor Curtin, and Robert Machemer. Ron found himself right at home in this exciting and stimulating environment. His papers with Don Gass on branch vein occlusion and the series of publications with Robert Machemer regarding vitreous surgery clearly set the standard for that day and established Ron as one of the up-and-coming retinal specialists who would lead the revolution in the diagnosis and management of retinal diseases. Ron had an incredible ability to analyze and organize, which, coupled with his hard work,

allowed him to establish monumental goals and then to accomplish them. At the same time, he could find humor in any situation, and he was always there to help his friends.

I fondly remember visiting Ron and his beautiful and charming wife, Alice, in Miami; they epitomized the most positive aspects of southern hospitality. Although none of us had income other than the stipend of a house officer while in training, we truly had great times together, and all of us knew that the world was our oyster. I was pleased to see that my young friend was taking up tennis in Miami and, characteristically, was going at it in a determined and organized manner. As in everything he did, he had infectious enthusiasm. There was no halfway about Ron Michels. However, he never achieved the prowess displayed by Alice in this sport! We always had great fun together, and I always eagerly anticipated every meeting with Ron and Alice, including the chance to stay with them every year for the annual Wilmer meeting.

It was with extremely mixed emotions that I left Baltimore, Wilmer, and many good friends to come to Los Angeles in 1974. Ron inherited my office at Wilmer and quickly established himself and the Wilmer Institute as leaders in vitreoretinal diseases. His series of papers on vitreoretinal surgery, beginning in the early 1970s, were truly outstanding contributions in the field of ophthalmology. He had a number of important papers published and provided important contributions to every major journal in ophthalmology. Among his major publications was the book, *Vitreous Surgery*, voted the medical book of the year for 1981. It is almost unbelievable that one individual could be awarded this prize twice, but Ron won it again for his outstanding book, *Retinal Detachment*, which was coauthored with Pat Wilkinson and Tom Rice and published in 1990.

Ron's curriculum vitae included some 280 contributions to the literature. His series of papers relating to diabetic retinopathy and the proper approaches to complications of vitreous surgery in diabetes have fundamentally influenced the practice of vitreoretinal surgery. His papers on complicated retinal detachments, proliferative vitreoretinopathy, and epiretinal membranes were major contributions to the field of vitreous surgery. His surgical fame, however, extended far beyond his manuscripts and lectures.

In the late 1970s, when the Cold War was at its most frigid, the Kremlin sought the best

vitreoretinal surgeon in the world to operate on one of their leaders. They asked Ron Michels to go to Moscow, where he and his good friend, Walter Stark (as his assistant), performed successful surgery for a macular pucker. As would be expected, considering the political climate of the time, it was requested that everything be kept secret, and only the Central Intelligence Agency was to be involved in the debriefing. Ron always enjoyed telling the story of his attempts to avoid the media and to separate Walter from them. A few years later, the scenario was replayed when an Afghan resistance hero sought care for his remaining eye, which was in a seemingly hopeless condition. Ron salvaged the eye. This Afghan hero, again thanks to Walter's promotional spirit, came away believing that Dr. Stark had saved his vision. Ron related these stories and others so well and with such humor and an obvious lack of rancor that they elicited nothing but good fellowship, especially from Walter. Ron was often cited for his work on behalf of Sugar Ray Leonard, whose retinal detachment he successfully repaired. Another boxer, Ernie Shavers, had a giant retinal tear. As with Leonard, Ron again performed the operation successfully. Ron was not an advocate of boxing, but he pointed out clearly and concisely the pathogenesis and pathoanatomy of these detachments that he had successfully treated.

Ron contributed greatly to the Wilmer Institute and its reputation for leadership in vitreoretinal diseases and surgery until September 1989, when he left to go into practice with Bert Glaser. He told me of the pleasure he took in this new approach and his enjoyment of his professional association with Bert, who freely gives credit to Ron for stimulating his career, first as a young resident and then as a fellow and faculty member of the vitreoretinal service at Wilmer and then in private practice together. Alice Michels has favored the concept of the Ronald G. Michels Fellowship Fund, which will fund vitreoretinal fellows throughout the world on a competitive basis. She has indicated that, because Ron profited so much from and took such pride in his Heed Fellowship, such a fund bearing his name and focusing on vitreoretinal diseases would most appeal to him among all the memorial possibilities.

I could discuss exhaustively the many accomplishments of Ron Michels on a professional level, but perhaps his most outstanding contributions were as an individual and human being at a personal level. For many years, I had the

pleasure of having Ron as my tennis partner at the annual Academy meeting, when he and I would take on Ron Smith and Pat Wilkinson. As any who saw us know, there was far more talk than talent on the tennis court. When Ron Smith would periodically try to employ his psychological warfare and head games, Ron Michels, with his proper club etiquette and being a true gentleman, could only marvel at some of the antics of the players he faced across the net. At the small postmatch dinner, euphemistically called the awards banquet, Ron would distinguish himself as the toastmaster, good-naturedly pointing out the athletic shortcomings and foibles of Drs. Smith and Wilkinson. Ron had a great sense of humor and was truly glib.

Throughout his illness, Ron showed the courage, fortitude, and genuine concern for his friends that characterized his friendships in life. Against a devastating and, ultimately, terminal illness, Ron marshaled his own remarkable strength and positive attitude. The inner confidence and conviction that allowed Ron to persuade patients to take on otherwise impossible operations, he applied to himself. He convinced himself that he would have a successful heart transplant that would allow him to carry on his life and work in ophthalmology. He was genuinely concerned about the sorrow of his friends when telling us of his illness. At the same time, by his positive attitude and indomitable will, he also caused us to believe that a heart transplant would be successful. In retrospect, it is still hard to believe that so many of us, as physicians, suspended rational thinking about the realities and difficulties of a heart transplant because Ron had assured us that it would work.

In the last few weeks of his life, Ron spoke to me with great pride of the accomplishments of

his family. He noted his son, Randy's, good record in school and of his accomplishments in golf and tennis. Many times, he stated how proud he was of Randy. His daughter, Allison, likewise, brought in ribbons, and Ron took great pleasure in his daughter. He spoke freely of his love for Alice and the great support she had been throughout his life and, particularly, during this illness.

Ron was truly extraordinary. His organization and ability to pull projects through to fruition suggest that, in some ways, he was bigger than life. In regard to the saying, "To him whom much is given is much expected," there is no question but that Ron was given far more talents and abilities than most. At the same time, we all recall that Ron gave to others far more than he took throughout his life. He truly was a giver who was committed to helping his fellow man. Whether a government leader in this or any other country, a captain of industry or a production line assembler, a multimillion dollar professional athlete or a Little League shortstop, all of Ron's patients received equal treatment, that is, the best. When working with him, we came to accept his exceptional performance as the norm. Even when observing him from a distance, one could see how truly extraordinary were his accomplishments. He was a dedicated and inspiring teacher, a skilled and caring ophthalmic surgeon, and a sensitive and loving family man and friend whose absence will be felt for many, many years.

A memorial service for Ron Michels was held on April 25, 1991, during the 50th anniversary meeting of the Wilmer Residents Association at the Johns Hopkins Medical Institute in Baltimore, Maryland.

STEPHEN J. RYAN

ABSTRACT DEPARTMENT

Edited by Michael A. Kass, M.D.

Epidemiologic evidence of a role for the antioxidant vitamins and carotenoids in cataract prevention. Jacques, P. F., and Chylack, L. T., Jr.: *Am. J. Clin. Nutr.* 53:352S, 1991.

CATARACT, VITAMIN C, VITAMIN E

The relationship between antioxidant nutrient status and senile cataract was examined in 77 subjects with cataracts and 35 control subjects with clear lenses. The subjects were classified as having low (below the 20th percentile), moderate (20th to 80th percentiles), and high levels (above the 80th percentile) of plasma nutrient and nutrient intake of vitamin C, vitamin E, and carotenoids. The odds ratio of cortical cataract among subjects with low plasma carotenoid levels was 7.2, and the odds ratio of posterior subcapsular cataract for subjects with low plasma vitamin C was 11.3. Low vitamin C intake was associated with an increased risk of cortical cataract (odds ratio, 3.7) and posterior subcapsular cataract (odds ratio, 11.0). Subjects who consumed fewer than 3.5 servings of fruit or vegetables per day had an increased risk of both cortical cataract (odds ratio, 5.0) and posterior subcapsular cataract (odds ratio, 12.9). These findings support the hypothesis that oxidation of lens proteins may play an important role in the pathogenesis of age-related cataract.—Michael A. Kass

A possible role for vitamins C and E in cataract prevention. Robertson, J. M.*, Donner, A. P., and Trevithick, J. R.: *Am. J. Clin. Nutr.* 53:346S, 1991.

CATARACT, VITAMIN C, VITAMIN E

Biochemical evidence suggests that oxidative stress caused by accumulation of free radicals is involved in the pathogenesis of senile cataracts. If so, appropriate amounts of the antioxidant vitamins C and E might be expected to prevent or retard the process. Such activity has been observed in several in vitro and in vivo studies of experimentally induced cataracts. A recent epidemiologic study found that cataract patients tended to have lower serum levels of

vitamins C, E, or carotenoids than did control subjects. The present investigation, which compared the self-reported consumption of supplementary vitamins by 175 cataract patients with that of 175 individually matched, cataract-free subjects, revealed that the latter group used significantly more supplementary vitamins C and E ($P = .01$ and $.004$, respectively). Because the results suggested a reduction in the risk of cataracts of at least 50%, a randomized, controlled trial of vitamin supplementation in cataract prevention may be warranted.—Authors' abstract

*Department of Epidemiology and Biostatistics, Faculty of Medicine, University of Western Ontario, London, Ontario, N6A 5C1, Canada.

Randomized single blind trial to compare the toxicity of subconjunctival gentamicin and cefuroxime in cataract surgery. Jenkins, C. D. G., McDonnell, P. J., and Spalton, D. J.*: *Br. J. Ophthalmol.* 74:734, 1990.

CATARACT SURGERY, SUBCONJUNCTIVAL GENTAMICIN, SUBCONJUNCTIVAL CEFUROXIME

Comparatively little attention has been paid to the conjunctival toxicity of antibiotics administered at the time of cataract surgery. We have observed the effect of subconjunctival gentamicin and cefuroxime injection, using color photography in a randomized single blind trial of 121 patients undergoing routine cataract surgery. Our results suggest that a hyperemic eye is likely to occur about twice as often in patients injected with gentamicin ($P < .001$). Gentamicin is associated with more pain post-operatively ($P < .05$). Significant manifestations of gentamicin toxicity are conjunctival edema and capillary closure. Cefuroxime has some theoretical advantages over gentamicin in its antibacterial spectrum.—Authors' abstract

*Medical Eye Unit, St. Thomas's Hospital, Lambeth Palace Rd., London SE1 7EH.

Precapsular film on the aging human lens. Precursor of pseudoexfoliation? Dark, A. J.,

and Streeten, B. W.*: Br. J. Ophthalmol. 74:717, 1990.

PSEUDOEXFOLIATION, FIBRILLIN, PRECAPSULAR FILM

In many older patients we observed a layer of subtle opacification on the anterior lens capsule, appearing as a ground glass film biomicroscopically. This precapsular film could be uniform but often had radial gray lines in the mid zone, holes in the paracentral region, and was occasionally rolled up in strings. Lens capsular material obtained at cataract extraction was studied in patients with and without the film. By scanning electron microscopy the precapsular film appeared as a friable, incomplete fibrillar layer, with rolling of the edges suggesting loose attachment. Ultrastructurally its component fibrils were from 3–6 nm in diameter, similar to the finer fibrils in pseudoexfoliation material. Like pseudoexfoliation material the layer stained positively for the elastic microfibril-associated protein, fibrillin, in a lens with radial striations. These similarities suggested that the two conditions have some relationship and that the precapsular film may be a precursor of pseudoexfoliation. Finding patches of the fibrillar network in some control patients implies that the precapsular film is common in patients of cataract age, though seldom detected clinically.—Authors' abstract

*Department of Pathology, Weiskotten Hall, SUNY Health Science Center, 766 Irving Ave., Syracuse, NY 13210.

Force necessary to fracture the orbital floor. Green, R. P., Jr.*, Peters, D. R., Shore, J. W., Fanton, J. W., and Davis, H.: Ophthalmic Plast. Reconstr. Surg. 6:211, 1990.

ORBITAL BLOW-OUT FRACTURE, HYDRAULIC MECHANISM, ANIMAL MODEL

Current thought on the pathophysiology of orbital wall fractures postulates either a "hydraulic" or a "buckling" mechanism. Evidence from cadaver, dried skull, and theoretical model studies supports both theories. No in vivo data, human or nonhuman primate, are available that quantitate the force necessary to fracture the orbital floor by either of the two mechanisms. We developed an apparatus that delivers

quantifiable force only to the globe, without occluding the orbital opening or striking the orbital rim. We used it on 11 anesthetized *Macaca fascicularis* monkeys. Following a single bilateral application, the orbits were exenterated, and the orbital walls and orbital contents were examined to determine the extent of injuries. Fractures were described, diagrammed, and photographed. Fracture of the orbital floor was consistently produced at and above a force of 2.08 J. Posterior ruptures of five eyes occurred over the same range. We provide the first accurate measurements of the force required to produce orbital blow-out fractures in a live primate model. We show that orbital floor fractures can occur at low energies with direct ocular trauma only ("pure" hydraulic mechanism). Orbital wall fractures failed to protect the globe from rupture in 23% of cases.—Authors' abstract

*USAFSAM/NGO, Brooks Air Force Base, TX 78235.

Color Doppler imaging in the management of intraocular tumors. Lieb, W. E., Shields, J. A.*, Cohen, S. M., Merton, D. A., Mitchell, D. G., Shields, C. L., and Goldberg, B. B.: Ophthalmology 97:1660, 1990.

COLOR DOPPLER ULTRASOUND, INTRAOCULAR TUMORS, IMAGING

Forty-four intraocular mass lesions were studied using a new, noninvasive ultrasound technique known as color Doppler imaging. This technique displays color-encoded Doppler flow information throughout a two-dimensional gray scale image thus providing selective analysis of Doppler spectra in small vessels using pulsed Doppler. Abnormal Doppler shifts were demonstrated within 39 neoplastic lesions studied, but Doppler shifts could not be detected in three tumor-simulating lesions. In a group of 12 choroidal melanomas studied after radiation therapy, lower Doppler shifts were seen compared with a group of 28 tumors before therapy. This change in Doppler shift may reflect the decreased vascular supply of the tumor. Color Doppler imaging may be of value as an additional useful tool in the diagnosis and management of intraocular tumors.—Authors' abstract

*Oncology Service, Wills Eye Hospital, 9th and Walnut Sts., Philadelphia, PA 19107.

Tonometer utilization, accuracy, and calibration under field conditions. Wessels, I. F.*, and Oh, Y.: Arch. Ophthalmol. 108:1709, 1990.

OFFICE TONOMETERS, CALIBRATION

A field survey conducted in 94 ophthalmologists' offices in our immediate area assessed the accuracy of tonometers in daily use. One hundred eighty-five instruments were examined: 127 were slit lamp mounted, 48 were hand held, and 10 were noncontact devices. Nineteen percent of applanation tonometers were outside the manufacturers' specifications (1 mm Hg of the calibration) and 4.5% were more than 2 mm Hg in error. The error was constant across the scale. Hand-held applanators were less accurate than those on slit lamps ($P < .02$); the latter demonstrated an association between accuracy and age ($P < .05$) and heavier use ($P < .01$). Annual recalibration was performed in 86% of instruments. Those practitioners who themselves performed the calibration had the most accurate instruments. Less than 15% knew how to perform the calibration check.—Authors' abstract

*Department of Ophthalmology, Loma Linda University, 11370 Anderson St., Ste. 1800, Loma Linda, CA 92354.

The impact of intraocular pressure on visual field loss in primary open angle glaucoma. Gramer, E.*, and Althaus, G.: Klin. Monatsbl. Augenheilkd. 197:218, 1990.

PRIMARY OPEN-ANGLE GLAUCOMA, VISUAL FIELD LOSS, INTRAOCULAR PRESSURE

There has been controversy about the extent to which increased intraocular pressure contributes to the visual field loss of open-angle glaucoma. A group of 300 patients underwent careful automated perimetry using program 31 of the Octopus perimeter. The total visual field loss as quantified with program Delta correlated with the maximum intraocular pressure recorded. In a second study, 54 patients with open-angle glaucoma and markedly asymmetric visual field loss were studied. The eyes with greater visual field loss had higher maximum intraocular pressures than the fellow eyes with lesser visual field loss. In a third study, 300 patients with primary open-angle glaucoma were divided into different groups on the basis

of maximum intraocular pressure recorded. Group 1 had a maximum intraocular pressure of less than 30 mm Hg; Group 2 had a maximum intraocular pressure of 30 to 38 mm Hg; and Group 3 had a maximum intraocular pressure of 37 mm Hg or more. With increasing intraocular pressure there was more diffuse loss of vision involving both the upper and lower visual fields. Thus, it appears that high intraocular pressure results in diffuse nerve fiber damage, whereas nonpressure-dependent risk factors are associated with more localized visual field damage.—Michael A. Kass

*Universitäts-Augenklinik Würzburg, Josef-Schneider-Straße 11, D-8700 Würzburg, Germany.

Peripheral contrast sensitivity in glaucoma and ocular hypertension. Falcão-Reis, F., O'Donoghue, E., Buceti, R., Hitchings, R. A., and Arden, G. B.*: Br. J. Ophthalmol. 74:712, 1990.

PERIPHERAL CONTRAST SENSITIVITY, OPEN-ANGLE GLAUCOMA, OCULAR HYPERTENSION

Previous studies have attempted to diagnose open-angle glaucoma on the basis of diminished central contrast sensitivity. Although losses in contrast sensitivity occur in patients with open-angle glaucoma, there is overlap with control subjects even when the grating pattern is modulated as a function of time. Since the earliest visual field loss in glaucoma occurs peripherally, it is reasonable to measure contrast sensitivity peripherally as well. Measurements of contrast sensitivity were made centrally and peripherally, at 10, 15, 20, and 25 degrees off-axis in each of the four meridians 45, 135, 225, and 315 degrees. A sine wave grating of 1.9 cycles per degree, reversing at 1 Hz was used. Patients with primary open-angle glaucoma and minimal visual field loss were compared to normal individuals and ocular hypertensive individuals, with the latter group being divided into high-, medium-, and low-risk groups. The patients with primary open-angle glaucoma had normal central contrast sensitivity, but at 20- and 25-degrees eccentricity the values for contrast sensitivity were more than 2 standard deviations above the normal mean. This was also the case for high-risk ocular hypertensive subjects but not for low-risk subjects. It is possible that a modification

of this technique may be a practical tool for glaucoma screening.—Michael A. Kass

*Electrodiagnostic Clinic, Moorfields Eye Hospital, City Rd., London EC1V 2PD.

Population and pedigree studies reveal a lack of association between the dopamine D₂ receptor gene and alcoholism. Bolos, A. M., Dean, M., Lucas-Derse, S., Ramsburg, M., Brown, G. L., and Goldman, D.*: JAMA 264:3156, 1990.

ALCOHOLISM, GENETIC PREDISPOSITION, DOPAMINE D₂ RECEPTOR GENE

Using the dopamine D₂ receptor clone lambda-hD2G1, Blum et al recently found that the D₂/Ta_q 1 allele (A1) was present in 69% of 35 deceased alcoholics but in only 20% of an equal number of controls. To assess this association further, we evaluated the D₂/Ta_q 1 polymorphism and a single-strand conformation polymorphism detected by polymerase chain reaction and nondenaturing gel electrophoresis (PCR-SSCP) of the 3' noncoding region of the D₂ receptor gene. We studied 40 unrelated white alcoholics, 127 racially matched controls, and two white pedigrees. The Schedule for Affective Disorders and Schizophrenia—Lifetime Version (SADS-L) clinical diagnostic interviews were rated blindly by two clinicians. The SADS-L interviews and other data were then used to ascertain diagnoses according to the Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition (DSM-III-R) criteria. Alcoholics were subtyped according to age of onset, severity, presence of antisocial personality, and family history. No significant differences in either D₂/Ta_q 1 or PCR-SSCP allele frequencies were observed between alcoholics, subpopulations of alcoholics, or controls. The PCR-SSCP polymorphism provided independent information against linkage at the D₂ receptor locus. Several recombinants between the D₂/Ta_q 1 locus and alcoholism were observed in two white families with an alcoholic parent who possessed the A1 allele. This study does not support a widespread or consistent association between the D₂ receptor gene and alcoholism.—Authors' abstract

*Section on Genetic Studies, Laboratory of Clinical Studies, National Institute on Alcohol Abuse and Alcoholism, 9000 Rockville Pike, Bldg. 10, Rm. 3C-102, Bethesda, MD 20892.

Environmental illness. A controlled study of 28 subjects with "20th century disease." Black, D. W.*, Rathe, A., and Goldstein, R. B.: JAMA 264:3166, 1990.

ENVIRONMENTAL ILLNESS, IMMUNOLOGIC DISEASE, PSYCHIATRIC DISORDER

Environmental illness is a polysymptomatic disorder believed by "clinical ecologists" to result from immune dysregulation brought on by common foods and chemicals. We systematically evaluated 28 subjects who had been assigned a diagnosis of environmental illness. The subjects indicated a strong interest in their diagnosis, were generally satisfied with their clinical ecologist, and were dissatisfied with traditional medical approaches. Subjects reported varying treatments, including dietary restrictions, avoidance of offending agents, and physical treatments. Using the Diagnostic Interview Schedule, we found that 15 (65%) of 23 subjects met criteria for a current or past mood, anxiety, or somatoform disorder compared with 13 (28%) of 48 age- and sex-matched community controls. We conclude that patients receiving this diagnosis may have one or more commonly recognized psychiatric disorders that could explain some or all of their symptoms.—Authors' abstract

*Department of Psychiatry, University of Iowa College of Medicine, 500 Newton Rd., Iowa City, IA 52242.

A randomized, double-blind trial of nystatin therapy for the candidiasis hypersensitivity syndrome. Dismukes, W. E.*, Wade, J. S., Lee, J. Y., Dockery, B. K., and Hain, J. D.: N. Engl. J. Med. 323:1717, 1990.

CANDIDIASIS HYPERSENSITIVITY SYNDROME, NYSTATIN THERAPY

Candida albicans infection has been proposed to cause a chronic hypersensitivity syndrome characterized by fatigue, premenstrual tension, gastrointestinal symptoms, and depression. Long-term antifungal therapy has been advocated as treatment for the syndrome, which is most often diagnosed in women with persistent or recurrent *Candida* vaginitis. To determine the efficacy of nystatin therapy in presumed candidiasis hypersensitivity syndrome, 42 premenopausal women who had a history of *Candida*

vaginitis were randomly assigned to one of four different combinations of nystatin or placebo, given orally or vaginally. The treatment regimens consisted of oral and vaginal nystatin, oral nystatin and vaginal placebo, oral placebo and vaginal nystatin, and oral placebo and vaginal placebo. Nystatin did not reduce the systemic symptoms significantly more than placebo. On average, the scores for systemic symptoms improved 25% with the three active-treatment regimens and 23% with the all-placebo regimen. As expected, the three active-treatment regimens were more effective than placebo in relieving vaginal symptoms. All four regimens reduced psychologic symptoms and global indexes of distress; there were no significant differences among the treatment regimens. Thus, in women with presumed candidiasis hypersensitivity syndrome, nystatin does not reduce systemic or psychologic symptoms significantly more than placebo. Consequently, the empiric recommendation of long-term nystatin therapy appears to be unwarranted in this situation.—Michael A. Kass

*Division of Infectious Diseases, Department of Medicine, University of Alabama Medical Center, Birmingham, AL 35294.

Reduced allergen-induced nasal congestion and leukotriene synthesis with an orally active 5-lipoxygenase inhibitor. Knapp, H. R.*: *N. Engl. J. Med.* 323:1745, 1990.

NASAL ALLERGY, LEUKOTRIENE SYNTHESIS, 5-LIPOXYGENASE INHIBITOR

It has been difficult to define the clinical importance of leukotrienes in human allergy, in part because there have been no selective 5-lipoxygenase inhibitors effective and safe for use in humans. Eight patients with allergic rhinitis underwent nasal challenge on two occasions after an oral dose of 800 mg of A-64077, a new 5-lipoxygenase inhibitor, or an identical-appearing placebo. Allergen-induced nasal congestion was significantly attenuated by A-64077. The drug inhibited synthesis of leukotriene B₄ and 5-hydroxyeicosatetraenoic acid in nasal fluids. In contrast, levels of prostaglandin D₂ and histamine were not reduced. These results provide direct evidence of an important role of the 5-lipoxygenase products of arachidonic acid in allergic rhinitis and support the notion that further experiments in this area

may lead to new therapeutic approaches to allergic disorders.—Michael A. Kass

*Division of Clinical Pharmacology, Department of Internal Medicine, University of Iowa Hospitals and Clinics, Iowa City, IA 52242.

Paraneoplastic pemphigus. An autoimmune mucocutaneous disease associated with neoplasia. Anhalt, G. J.*, Kim, S. C., Stanley, J. R., Korman, N. J., Jabs, D. A., Kory, M., Izumi, H., Ratrie, H., III, Mutasim, D., Ariss-Abdo, L., and Labib, R. S.: *N. Engl. J. Med.* 323:1729, 1990.

PEMPHIGUS, NEOPLASM

The term pemphigus refers to a group of mucocutaneous diseases that are characterized by intraepithelial blisters. The blisters are caused by a loss of normal cell-to-cell adhesion and are associated with autoantibodies against cell-surface proteins of stratified squamous epithelia. Five patients were examined who had underlying neoplasms and who developed painful mucosal ulcerations and polymorphous skin lesions. The patients eventually developed blistering eruptions on the trunk and extremities. Histologic examination showed vacuolization of epidermal basal cells, keratinocyte necrosis, and acantholysis. Immunofluorescence testing disclosed atypical pemphiguslike autoantibodies in perilesional epithelium and serum from all five patients. Three of the five patients developed vesicals and bleeding erosions of the conjunctiva. The authors proposed the term "paraneoplastic pemphigus" for this disease.—Michael A. Kass

*Department of Dermatology, Johns Hopkins University, 800 N. Wolfe St., Baltimore, MD 21205.

Time course of thymoxamine reversal of phenylephrine-induced mydriasis. Wright, M. M., Skuta, G. L.*, Drake, M. V., Chang, L. F., Rabbani, R., Musch, D. C., and Teikari, J.: *Arch. Ophthalmol.* 108:1729, 1990.

THYMOXAMINE, PHENYLEPHRINE-INDUCED MYDRIASIS

We conducted a randomized, double-masked, paired comparison of 0.1% thymoxamine vs

placebo for the reversal of phenylephrine-induced mydriasis. Mydriasis was induced with 2.5% phenylephrine in each eye of 74 subjects (148 eyes). Each subject then received 0.1% thymoxamine in one eye and placebo in the other eye. Pupillary measurements were obtained at regular intervals during the ensuing 8 hours. At all intervals, a greater percentage of thymoxamine-treated eyes returned to baseline pupillary diameters compared with placebo-treated eyes ($P \leq .01$). For subjects in whom both pupils returned to baseline, thymoxamine-treated eyes returned to baseline in a mean of 2.2 hours, vs 5.2 hours for placebo ($P < .0001$). Among thymoxamine-treated eyes, those with light irides responded more rapidly than those with dark irides, returning to baseline in 1.6 vs 2.8 hours, respectively ($P = .0046$). After constriction to baseline pupillary diameter had been achieved, no patients experienced a rebound dilation.—Authors' abstract

*W. K. Kellogg Eye Center, 1000 Wall St., Ann Arbor, MI 48105.

Comparison of non-mydriatic retinal photography with ophthalmoscopy in 2159 patients. Mobile retinal camera study. Taylor, R.*, Lovelock, L., Tunbridge, W. M. G., Alberti, K. G. M. M., Brackenridge, R. G., Stephenson, P., and Young, E.: *Br. Med. J.* 301:1243, 1990.

DIABETIC RETINOPATHY, SCREENING, OCULAR EXAMINATION, NONMYDRIATIC RETINAL PHOTOGRAPHY

Diabetic retinopathy remains a common cause of blindness despite the availability of effective treatment. Physicians should be trained so that they can identify retinopathy in its early stages when treatment is most effective. A cohort group of 2,159 adult diabetic patients underwent retinal photography using a non-mydriatic camera and then had direct ophthalmoscopy after pupillary dilation. Each patient was examined by his or her usual physician. Retinal photography and ophthalmoscopy were equally effective in detecting new vessels. Photography, however, was far more sensitive in detecting diabetic maculopathy. Eventually 38 eyes received laser treatment for maculopathy after detection by camera screening compared with 17 eyes after ophthalmoscopic detection ($P < .01$). Photography underestimated

the numbers of microaneurysms and hemorrhages, whereas ophthalmoscopy underestimated the number of hard exudates. Overall it appeared that nonmydriatic retinal photography is at least as good as ophthalmoscopy with mydriasis for screening patients in diabetic clinics. It is possible that the availability of feedback from photography will improve physicians' skills at ophthalmology.—Michael A. Kass

*Division of Endocrinology, Department of Internal Medicine, Yale Medical School, 333 Cedar St., New Haven, CT 06510-8056.

Significance of cytotoxic eye muscle antibodies in patients with thyroid-associated ophthalmopathy. Hiromatsu, Y., Cadarso, L., Salvi, M., and Wall, J. R.*: *Autoimmunity* 5:205, 1990.

EXTRAOCULAR MUSCLE ANTIBODIES, THYROID-ASSOCIATED OPHTHALMOPATHY

There is considerable evidence that thyroid-associated ophthalmopathy is an autoimmune disorder. A number of studies have detected antibodies against extraocular muscle antigens and have noted infiltration of muscle and orbital connective tissue by lymphocytes and monocytes. The authors sought to correlate the clinical severity of thyroid-associated ophthalmopathy with the level of extraocular muscle reactive antibodies as measured in an antibody-dependent, cell-mediated cytotoxicity assay. Positive assays were noted in 21 of 42 patients with thyroid-associated ophthalmopathy, and in eight of 14 patients with Graves' disease without evident ocular involvement but in none of 12 normal control subjects. There were positive correlations between levels of extraocular muscle-reactive cytotoxic antibodies and the severity of the ocular disease as quantified by the American Thyroid Association classification. There were also significant correlations between the levels of extraocular muscle-reactive cytotoxic antibodies and intraocular pressure measured in primary position and in downgaze but not with the degree of proptosis. These results suggest that cytotoxic antibodies as detected in an antibody-dependent, cell-mediated cytotoxicity assay may play a role in the extraocular muscle damage of thyroid-associated ophthalmopathy and that

measurement of the cytotoxic antibodies may provide a useful clinical test.—Michael A. Kass

*Thyroid Research Unit, Montreal General Hospital Research Institute, 1650 Cedar Ave., Montreal, Quebec, H3G 1A4, Canada.

Detection of a human intracisternal A-type retroviral particle antigenically related to HIV. Garry, R. F.*, Fermin, C. D., Hart, D. J., Alexander, S. S., Donehower, L. A., Luo-Zhang, H.: *Science* 250:1127, 1990.

SJÖGREN'S SYNDROME, RETROVIRAL PARTICLE

Sjögren's syndrome is an autoimmune disease that is characterized by dryness of the mouth and eyes. The loss of salivary and lacrimal gland function is accompanied by lymphocytic infiltration. Because similar symptoms and glandular pathology are observed in certain persons infected with human immunodeficiency virus (HIV), a search was initiated for a possible retroviral etiology in this syndrome. A human intracisternal A-type retroviral particle that is antigenically related to HIV was detected in lymphoblastoid cells exposed to homogenates of salivary tissue from patients with Sjögren's syndrome. Comparison of this retroviral particle to HIV indicates that they are distinguishable by several ultrastructural, physical, and enzymatic criteria.—Authors' abstract

*Department of Microbiology and Immunology, Tulane University School of Medicine, New Orleans, LA 70112.

Subretinal neovascular membranes associated with chronic membranoproliferative glomerulonephritis type II. Leys, A.*, Michielsens, B., Leys, M., Vanrenterghem, Y., Missotten, L., and Van Damme, B.: *Graefes Arch. Clin. Exp. Ophthalmol.* 228:499, 1990.

SUBRETINAL NEOVASCULAR MEMBRANE, MEMBRANOPROLIFERATIVE GLOMERULONEPHRITIS TYPE II

Subretinal neovascular membranes were observed in three patients with chronic membranoproliferative glomerulonephritis type II (dense deposit disease). The first signs of glomerulonephritis occurred at respective ages of 13, 10 and 10 years; subretinal neovascular membranes were noted at respective ages of 25, 32 and 32 years. All patients had bilateral, widespread retinal pigment epithelial abnormalities. Our findings indicate that subretinal neovascularization is a complication of dense deposit disease. In one patient, the early recognition and laser treatment of an extrafoveal subretinal neovascular membrane prevented further loss of vision.—Authors' abstract

*Department of Ophthalmology, K. U. Leuven, Capucijnenvoer 33, B-3000 Leuven, Belgium.

NEWS ITEMS

Send News Items to
American Journal of Ophthalmology
435 N. Michigan Ave., Suite 1415
Chicago, IL 60611

The Journal invites readers to submit announcements concerning meetings, postgraduate courses, lectures, honors, and appointments. Each item must be typed double-spaced on bond paper with 1½-inch margins. Only one news item should be submitted on each page. Announcements concerning meetings and courses must contain the title, location, dates, sponsors, and address required for additional information. Each item must not exceed 75 words in length and be prepared in narrative, not outline, form. Announcements of meetings and courses must be received at least four months before the event.

International Symposium on Graves' Ophthalmopathy

An International Symposium on Graves' Ophthalmopathy will be held Aug. 23 and 24, 1991, in Amsterdam, The Netherlands. For more information, write Amsterdam Thyroid Club, c/o W. M. Wiersinga, M.D., Dept. of Endocrinology, F5-258, Academic Medical Center, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands.

Canadian Implant Association: Application of New Technology to Clinic Practice

The Canadian Implant Association will hold its 17th Annual Meeting, Application of New Technology to Clinic Practice, in Montreal, Canada, July 14 and 15, 1991. For further information, write Marvin Kwitko, M.D., Program Chairman, 5591 Cote des Neiges Rd., Ste. 1, Montreal, Quebec, Canada H3T 1Y8; telephone (514) 735-1133.

First World Congress of Cellular and Molecular Biology

The First World Congress of Cellular and Molecular Biology will be held in Paris and Versailles, Palais des Congrès, Sept. 1-7, 1991. For further information, write Prof. R. Wegmann, Editor-in-Chief, Institut D'Histochimie Medicale, Universite Pierre Et Marie Curie, 7 Quai St. Bernard, 75005 Paris, France.

Association for Research in Vision and Ophthalmology

The recipients of awards by the Association for Research in Vision and Ophthalmology for 1991 are as follows: The Proctor Medal—Robert B. Nussenblatt, M.D., National Eye Institute, and Waldon B. Wacker, Ph.D., Universi-

ty of Louisville; Friedenwald Award—Richard F. Brubaker, M.D., Mayo Clinic; Cogan Award—Jay S. Pepose, M.D., Ph.D., Washington University; Weisenfeld Award—Bradley R. Straatsma, M.D., Jules Stein Eye Institute.

Baylor Ophthalmology Alumni Association: 28th Annual Meeting

The Baylor Ophthalmology Alumni Association will hold its 28th Annual Meeting in Houston, Texas, June 6-8, 1991. For further information, write Diane Nolte, Program Coordinator, Cullen Eye Institute, 6501 Fannin, NC-200, Houston, TX 77030; telephone (713) 798-6443.

Humana Hospital Audubon: Eighth Annual Ophthalmology Seminar

The Humana Hospital Audubon will sponsor its Eighth Annual Ophthalmology Seminar, Lasers and Beyond, Sept. 14, 1991, in Louisville, Kentucky. For further information, write Norman D. Radtke, M.D., 240 Audubon Medical Plaza, Louisville, KY 40217; telephone (502) 636-2823.

Manhattan Eye, Ear & Throat Hospital: Masters of Cataract Surgery

The Department of Ophthalmology at the Manhattan Eye, Ear & Throat Hospital will hold the Masters of Cataract Surgery, June 7 and 8, 1991, in New York City. For further information, write Kimberly Corbin, Course Coordinator, Dept. of Ophthalmology, Manhattan Eye, Ear & Throat Hospital, 210 E. 64th St., New York, NY 10021; telephone (212) 605-3761; fax (212) 753-7699.

Medical College of Wisconsin: Current Concepts in Ophthalmology

The Eye Institute of the Medical College of Wisconsin will hold its annual Fall Symposium, Current Concepts in Ophthalmology, Nov. 8 and 9, 1991. For further information, write Tammy Conant, The Eye Institute, 8700 W. Wisconsin Ave., Milwaukee, WI 53226; telephone (414) 257-5102.

Phillips Eye Institute Center for Teaching & Research: Penetrating Keratoplasty/Eye Banking

The Phillips Eye Institute Center for Teaching & Research is sponsoring Penetrating Keratoplasty/Eye Banking, a surgical skills-transfer

workshop, July 15, 1991. For more information, write Mary Strazz, Phillips Eye Institute, 2215 Park Ave., Minneapolis, MN 55404; telephone (612) 336-5650.

San Diego Fluorescein and Laser Workshop

Alcon Surgical, Inc., will sponsor The San Diego Fluorescein and Laser Workshop for General Ophthalmologists July 12 and 13, 1991, in San Diego, California. For further information, write Tara Wilson, 12630 Monte Vista Rd., Ste. 104, Poway, CA 92064; telephone (619) 451-1911.

Stanford University: Basic Science Course

Stanford University's Department of Ophthalmology will offer a Basic Science Course, July 1-Aug. 29, 1991. For further information, write Peter R. Egbert, M.D., Dept. of Ophthalmology, A-157; Stanford Medical Center, Stanford, CA 94305-5308; telephone Susan Marsh (415) 725-7269.

University of Illinois at Chicago Eye Center: Contact Lens Course

The University of Illinois at Chicago Eye Center is sponsoring a contact lens course: Basic and Advanced Topics, June 21 and 22, 1991, at the University of Illinois Hospital Eye and Ear Infirmary in Chicago. For more information, write Sue Talbert, Sr. Program Coordinator, University of Illinois at Chicago, 912 S. Wood St., 2nd Fl., Chicago, IL 60612; telephone (312) 996-5225; fax (312) 996-5227.

Personal

David A. Hiles

David A. Hiles, M.D., has recently accepted a full-time position as director of Pediatric Ophthalmology Services at Children's Hospital of Pittsburgh and chief of the Division of Pediatric Ophthalmology at the University of Pittsburgh School of Medicine.

VOLUME 111

JUNE 15

1991

Acc 97/93

AMERICAN JOURNAL OF OPHTHALMOLOGY

Monthly since 1884

Index Issue

• ORIGINAL ARTICLES

Acute Multifocal Inner Retinitis

Foster, Gutman, Meyers, Lowder

Unilateral Frosted Branch Angiitis

Sugin, Henderly, Friedman, Jampol, Doyle

Fortified Antibiotics

Bowe, Snyder, Eiferman

Conjunctival Necrosis After Topical Aminoglycosides

Davison, Tuft, Dart

Isolated Conjunctival Neurofibromas

Kalina, Bartley, Campbell, Buettner

Ocular Pigmentation and Cardiac Myxoma

Kennedy, Flanagan, Eagle, Carney

Cocaine Screening After Lacrimal Surgery

Cruz, Patrinely, Reyna, King

Palpebral Fissure and Adrenergic Drugs

Munden, Kardon, Denison, Carter

Antiglaucoma Drugs and Resolution Perimetry

Martin-Boglund, Graves, Wanger

Pseudophakic Pupillary Block in Children

Vajpayee, Angra, Titiyal, Sharma, Chhabra

Dissemination of Optic Pathway Gliomas

Bruggers, Friedman, Phillips, Wiener, Hockenberger, Oakes, Buckley

Optic Nerve Sheath Decompression

Spoor, Wilkinson, Ramocki

MRI in Optic Nerve Gliomas

Imes, Hoyt

Effect of Flurbiprofen on Miosis

Holmes, Jay

Endothelial Cell Density and Allograft Rejection

Musch, Schwartz, Fitzgerald-Shelton, Sugar, Meyer

Keratoplasty and Intraocular Lens Fixation

Davis, Best, Gilbert

Leber's Hereditary Optic Neuropathy

Newman, Lott, Wallace

• PERSPECTIVES

Lacrimal Gland Epidermal Growth Factor

Wilson

Disposable Soft Contact Lenses

John

• LETTERS TO THE JOURNAL

Dacryocystitis after punctal occlusion

Glatt

Macular edema and AIDS

Palestine, Frishberg

Cranial nerve palsies after embolization

Sabates, Tsai, Sabates, Blitstein

Cavernous sinus syndrome after retrobulbar anesthesia

Pearson, Solomon, Smith, Epstein

Retinopathy in human vitamin E deficiency

Berger, Tychsen, Rosenblum

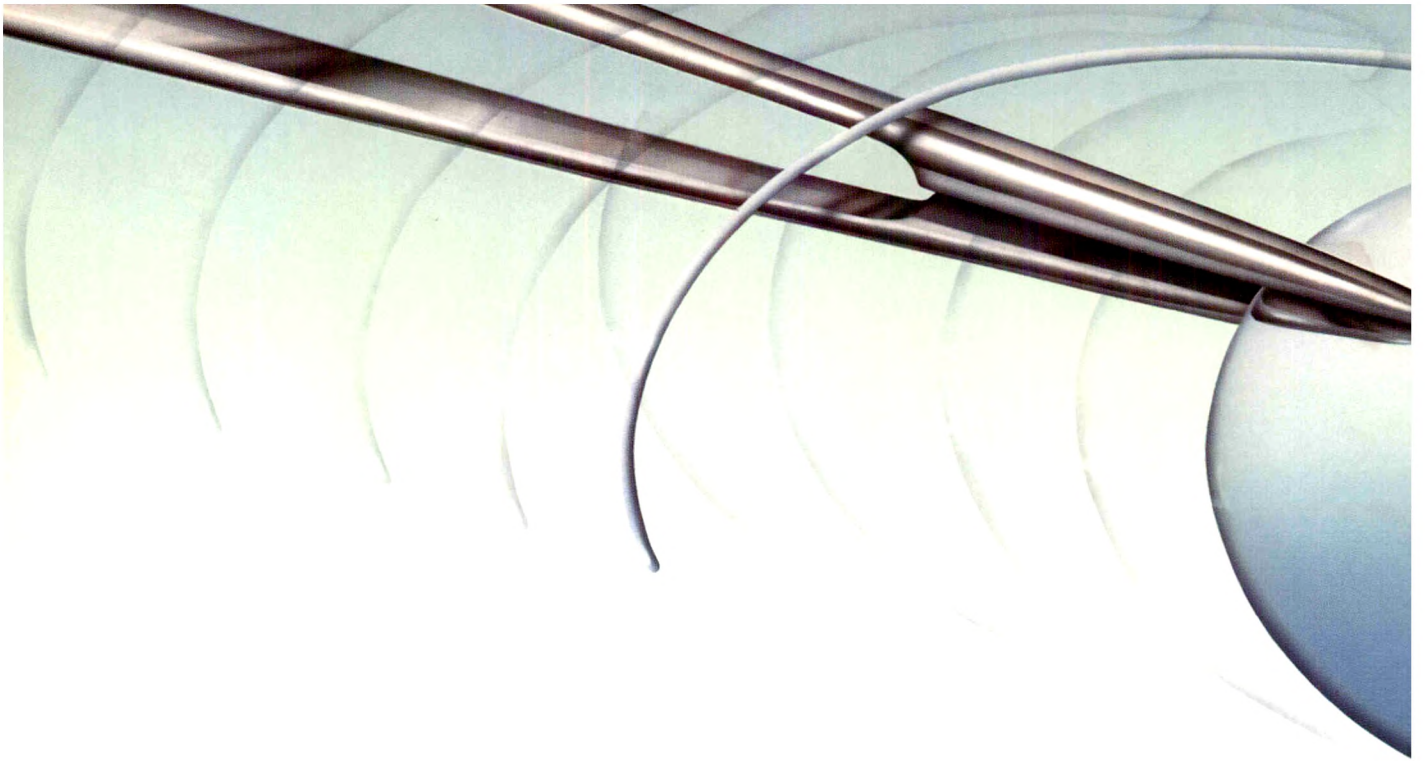
Keratoconus and congenital hip dysplasia

Nucci, Brancato

Flexible iris retractor

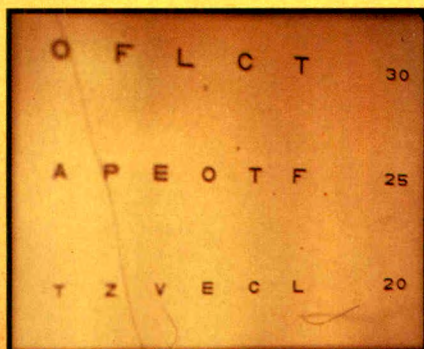
de Juan, Hickingbotham

AIO®



Viscoelastic
penetration
this dynamic is
the newest thing
you'll notice

Have you memorized this?



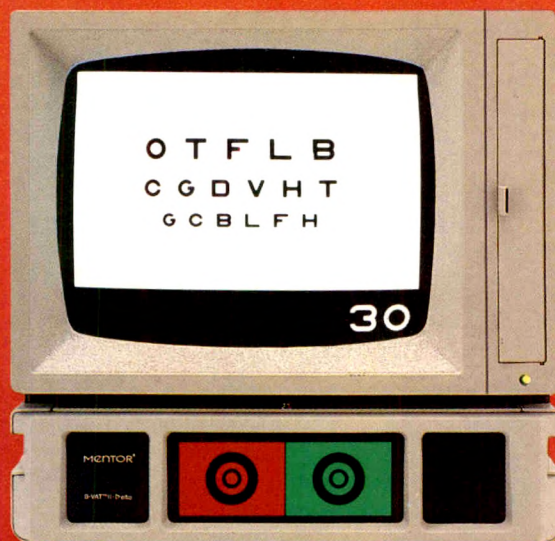
... so have your patients

Test their vision - not their memory



MENTOR® B-VAT™ II- ▶ elta Video Acuity Tester

- **Randomized letter presentation**
- **Economical** - little more than the cost of some projectors. Performs basic tests and can be upgraded with corded LCD readout hand controller.
- **Convenience of cordless IR remote control**



- **Faster** - less patient fatigue
- **More accurate than projectors**
- **Versatile** - specialized tests built-in (contrast sensitivity); can be upgraded (binocular vision tests)

The B-VAT II- ▶ elta is the newest member of the B-VAT II family:

B-VAT II - advanced testing capabilities

B-VAT II-SG - adds sinusoidal gratings for contrast sensitivity tests

BVS™ BINOCULAR VISION SYSTEM - stereo acuity testing capacity in an upgrade for any B-VAT II unit



MENTOR O&O INC.

3000 Longwater Drive, Norwell, MA 02061-1610

1-800-992-7557

TABLE OF CONTENTS

ORIGINAL ARTICLES

Acute multifocal inner retinitis

Robert E. Foster, Froncie A. Gutman, Sanford M. Meyers, and Careen Y. Lowder 673

Unilateral frosted branch angiitis

Stephanie L. Sugin, Dale E. Henderly, Scott M. Friedman, Lee M. Jampol, and J. William Doyle 682

An in vitro study of the potency and stability of fortified ophthalmic antibiotic preparations

Brian E. Bowe, James W. Snyder, and Richard A. Eiferman 686

Conjunctival necrosis after administration of topical fortified aminoglycosides

C. R. Davison, S. J. Tuft, and J. K. G. Dart 690

Isolated neurofibromas of the conjunctiva

Paul H. Kalina, George B. Bartley, R. Jean Campbell, and Helmut Buettner 694

The Carney complex with ocular signs suggestive of cardiac myxoma

Robert H. Kennedy, Joseph C. Flanagan, Ralph C. Eagle, Jr., and J. Aidan Carney 699

Urine drug screening for cocaine after lacrimal surgery

Oscar A. Cruz, James R. Patrinely, George S. Reyna, and J. W. King 703

Palpebral fissure responses to topical adrenergic drugs

Paul M. Munden, Randy H. Kardon, Chad E. Denison, and Keith D. Carter 706

The effect of topical antiglaucoma drugs on the results of high-pass resolution perimetry

Lene M. Martin-Boglund, Adrienne Graves, and Peter Wanger 711

Pseudophakic pupillary-block glaucoma in children

R. B. Vajpayee, S. K. Angra, J. S. Titiyal, Y. R. Sharma, and V. K. Chhabra 715

Leptomeningeal dissemination of optic pathway gliomas in three children

Carol S. Bruggers, Henry S. Friedman, Peter C. Phillips, M. David Wiener, Beverly Hockenberger, W. Jerry Oakes, and Edward G. Buckley 719

Optic nerve sheath decompression for the treatment of progressive nonarteritic ischemic optic neuropathy

Thomas C. Spoor, Michael J. Wilkinson, and John M. Ramocki 724

Magnetic resonance imaging signs of optic nerve gliomas in neurofibromatosis 1

Richard K. Imes and William F. Hoyt 729

The effect of preoperative flurbiprofen on miosis produced by acetylcholine during cataract surgery

Jonathan M. Holmes and Walter M. Jay 735

The effect of allograft rejection after penetrating keratoplasty on central endothelial cell density

David C. Musch, Ann E. Schwartz, Karen Fitzgerald-Shelton, Alan Sugar, and Roger F. Meyer 739

Comparison of intraocular lens fixation techniques performed during penetrating keratoplasty

Richard M. Davis, Douglas Best, and Gregory E. Gilbert 743

The clinical characteristics of pedigrees of Leber's hereditary optic neuropathy with the 11778 mutation

Nancy J. Newman, Marie T. Lott, and Douglas C. Wallace 750

PERSPECTIVES

Lacrimal gland epidermal growth factor production and the ocular surface

Steven E. Wilson 763

How safe are disposable soft contact lenses?

Thomas John 766

LETTERS TO THE JOURNAL

Acute dacryocystitis after punctal occlusion for keratoconjunctivitis sicca. Herbert J. Glatt, 769. Macular edema in acquired immunodeficiency syndrome-related microvasculopathy. Alan G. Palestine and Benjamin Frishberg, 770. Transient cranial nerve palsies after cavernous sinus fistula embolization. Felix N. Sabates, Jr., Fong Tsai, Nelson R. Sabates, and Bryan Blitstein, 771. Contralateral cavernous sinus syndrome after retrobulbar anesthetic injection. P. Andrew Pearson, Kerry D. Solomon, Thomas J. Smith, and Avrom D. Epstein, 773. Retinopathy in human vitamin E deficiency. Adam S. Berger, Lawrence Tyche, and Jerry L. Rosenblum, 774. Keratoconus and congenital hip dysplasia. Paolo Nucci and Rosario Brancato, 775. Flexible iris retractor. Eugene de Juan, Jr., and Dyson Hickingbotham, 776.

BOOK REVIEWS

Cosmetic Blepharoplasty (Stephen L. Bosniak). Reviewed by Michael Patipa, 778. Ptosis, ed. 4 (Michael Callahan and Crowell Beard). Reviewed by Jonathan J. Dutton, 778. Color Atlas of Ophthalmic Surgery.

(Table of Contents continued on Advertising Page 8)



Akorn

**TOPS THEM ALL
WITH COMPLYING
COLORS**

When the American Academy of Ophthalmology requested pharmaceutical manufacturers to provide color-coded caps with all ophthalmic preparations, AKORN responded immediately. That's why AK-Sulf and AK-Pred are available with the tan and pink caps according to the AAO's recommendations. And the rest of AKORN's line of quality, lower cost medications will have color-coded caps in the very near future.

More and more physicians are prescribing AKORN, and the reason is clear. No other company responds faster and gives better service. AKORN. . . our products produce results and reduce costs. That's a promise.

AK-SULF®

Akorn, Inc.

100 Akorn Drive, Abita Springs, LA 70420

1-800-535-7155

In Louisiana 1-800-344-2291

FAX 504-893-1257

NASDAQ Symbol: AKRN

AK-PRED®

TABLE OF CONTENTS (continued from Advertising page 6)

Strabismus (Kenneth W. Wright). Reviewed by Ronald V. Keech, 779. **The History of Ophthalmology**, vol. 9. **The First and Second Half of the Nineteenth Century** (Julius Hirschberg). Reviewed by Frank W. Newell, 779. **EndNote Plus**. Reviewed by W. L. M. Alward, 780. **The Best in Medical Humor** (Howard J. Bennett), 781. **Eye Care in Developing Nations**, ed. 2 (Larry Schwab), 781. **The Eye in Systemic Disease**, ed. 2 (Jack J. Kanski and Dafydd J. Thomas), 781. **Graves' Ophthalmopathy** (Edited by Jack R. Wall and Jacques How), 781. **How to Write and Publish Papers in the Medical Sciences**, ed. 2 (Edited by Edward J. Huth), 781. **Les Strabismes**. Tome Premier. **Les Divergences Oculaires** (R.

Pigassou-Albouy), 782. **Ophthalmology Oral History Series. A Link With Our Past. An Interview With David Glendenning Cogan, M.D.** (Sally Smith Hughes), 782. **Optics, Physiology and Vision** (Edited by Suzanne P. McKee and Ken Nakayama), 782. **Phacoemulsification Surgery** (Edited by Terence M. Devine and William Banko), 782.

ABSTRACTS 783

NEWS ITEMS 791

CORRECTION 792

CLASSIFIEDS Begins on Advertising 47

COPYRIGHT TRANSFER Advertising 20

INSTRUCTIONS TO AUTHORS Advertising 50

PRODUCTS AND SERVICES Begins on Advertising 40

ADVERTISING INDEX Advertising 54

INDEX i

PUBLICATION STAFF

MARY L. BORYSEWICZ
Executive Managing Editor

LINDA G. CLAUSEN
Records Manager

KAREN D. JOHNSON
Manuscript Editor

MOLLY MELICK
Assistant to the Editor

DIANN J. MARQUIS
Editorial Assistant

MICHAEL J. LUND
Subscription Correspondent

LYNN ANN LINDVIG
AND
RENEE L. KASTAR
Sales and Production

acc 9/93

Acute Multifocal Inner Retinitis

Robert E. Foster, M.D., Froncie A. Gutman, M.D., Sanford M. Meyers, M.D.,
and Careen Y. Lowder, M.D.

Two patients developed acute changes in vision two to four weeks after a febrile illness. On ophthalmic examination, each patient had bilateral vitreitis without anterior segment inflammation and multiple, bilateral, round, yellow-white inner retinal lesions that were located in the posterior pole and midperiphery. Laboratory tests did not contribute to a diagnosis. Symptomatic visual loss was caused by neuroretinitis and serous retinal detachment in one patient and by an occluded branch retinal artery in the other. The multifocal retinal lesions resolved gradually without treatment over several months with minimal or no residual retinal changes. Acute multifocal inner retinal lesions may be associated with a preceding nonspecific viral illness and may cause a sudden change in vision if associated with neuroretinitis, serous retinal detachment, or retinal vessel occlusion. We have termed this constellation of ophthalmic findings acute multifocal inner retinitis.

NUMEROUS INVESTIGATORS have described multifocal inflammatory processes involving the retina and choroid. Several of these disorders have been associated with a preceding nonspecific febrile illness, which has led some authors to postulate infection as a cause. We studied the clinical and angiographic characteristics of two patients with acute change in vision and bilateral, multifocal inner retinal lesions. Visual symptoms were related to neuroretinitis and serous retinal detachment of the macula in one patient and an occluded branch retinal artery in the other. Both patients had had a recent febrile

illness. In each case, the multifocal retinal lesions resolved gradually without treatment, although a few of the more severe lesions resulted in a mild focal retinal pigment epithelial disturbance or a small chorioretinal scar. Although an infectious source was considered, laboratory testing did not identify a specific cause.

Case Reports

Case 1

A 15-year-old girl had decreased vision in her left eye. Four weeks previously, she had had a fever of 38.8 C with mild, bilateral retro-orbital headaches. Six days before the examination, she developed a scotoma in the central vision in her left eye. Her medical history showed tonsillitis and varicella as a child. She was not taking any medications. A physical examination identified a 0.5-cm posterior cervical lymph node and no skin rash. Initial ophthalmic examination disclosed visual acuity of R.E.: 20/20 and L.E.: 20/200. There was a left relative afferent pupillary defect. Goldmann visual field testing showed a relatively dense superior centrocecal scotoma in the left eye. Slit-lamp biomicroscopy disclosed a moderate, bilateral, posterior vitreous cellular reaction without anterior segment inflammation. Ophthalmoscopy in the left eye disclosed a swollen, hyperemic disk with a white lesion along its inferotemporal border, dilated and tortuous branch retinal veins, and a serous retinal detachment extending from the disk to the macula (Fig. 1).

The disk and vessels of the right eye appeared normal. There were multiple, bilateral (five right eye, eight left eye) inner retinal lesions, which were small (100 to 200 μ m), yellow-white, round, and distributed in the posterior pole and midperipheral retina (Figs. 1 and 2). The stereoscopic fluorescein angiogram disclosed moderate leakage from the disk in the left eye that was most intense at the inferotemporal pole and minimal leakage into the adja-

Accepted for publication Feb. 21, 1991.

From the Department of Ophthalmology, Cleveland Clinic Foundation, Cleveland, Ohio. This study was presented in part at the annual meeting of the Retina Society, Key Largo, Florida, Oct. 5, 1990.

Reprint requests to Froncie A. Gutman, M.D., Department of Ophthalmology A31, Cleveland Clinic Foundation, One Clinic Center, 9500 Euclid Ave., Cleveland, OH 44195-5024.

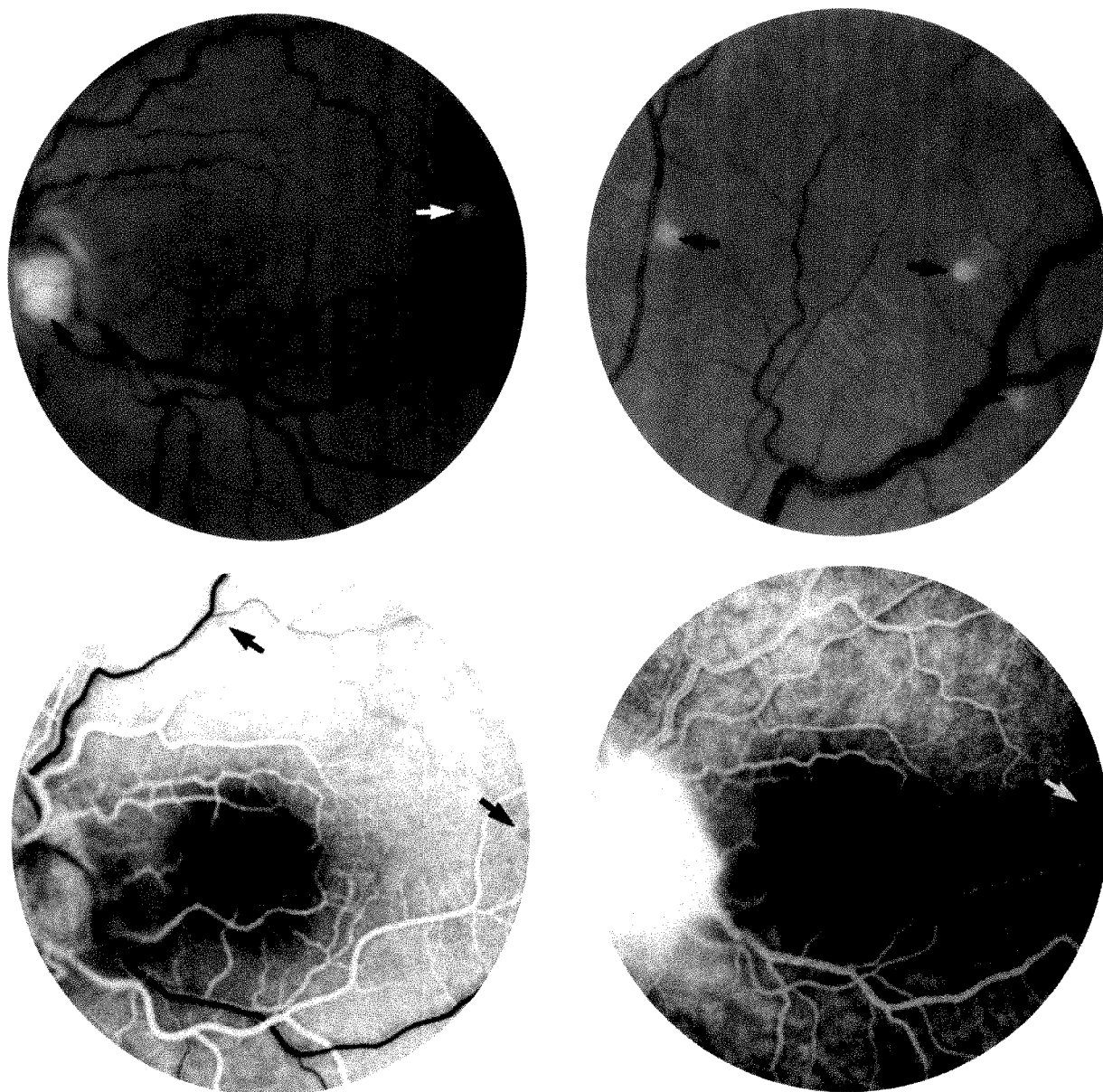


Fig. 1 (Foster and associates). Case 1, left eye. Top left, Disk edema and hyperemia and serous retinal detachment involving the macula with inner retinal lesions temporal to fovea (white arrow) and at inferotemporal disk border (black arrow). Top right, Three inner retinal lesions superior to disk (arrows). Bottom left, Early-phase fluorescein angiogram showing leakage from inferotemporal disk, corresponding to white lesion. Note relative central hypofluorescence with hyperfluorescent border that corresponds to inner retinal lesions (arrows). Bottom right, Late-phase angiogram demonstrating central hypofluorescence and hyperfluorescent rim corresponding to retinal lesion (arrow).

cent serous retinal detachment (Fig. 1). At the site of the inner retinal lesions there was a subtle central hypofluorescence with a faint hyperfluorescent rim in the early phases of the angiogram (Fig. 1). Late phases demonstrated increased marginal hyperfluorescence and irregular central hypofluorescence (Figs. 1 and

2). Clinical examination with a Goldmann contact lens confirmed the inner retinal location of the white retinal lesions.

The initial diagnosis was neuroretinitis of the left eye and bilateral multifocal retinitis of probable infectious origin. Ten days later, visual acuity in the left eye improved to 20/80.

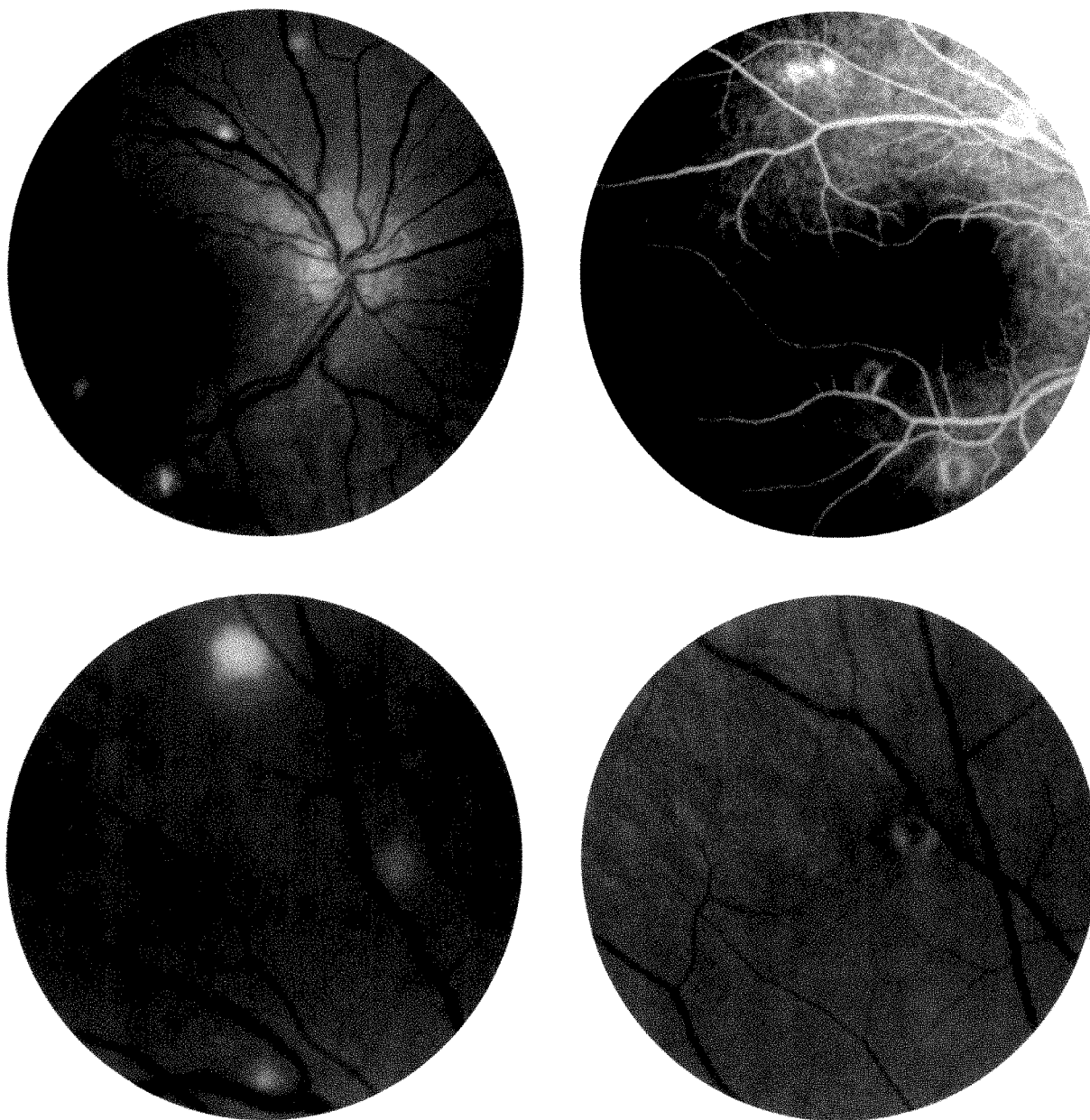


Fig. 2 (Foster and associates). Case 1, right eye. Top left, Four inner retinal lesions. Top right, Late-phase angiogram demonstrating irregular central hypofluorescence and hyperfluorescent rim corresponding to retinal lesions. Bottom left, Enlarged view of three inner retinal lesions superotemporal to disk. Bottom right, Twenty-three months later, an enlarged view of a small chorioretinal scar corresponding to the previous more intense superior retinal lesion shown at bottom left.

Examination disclosed decreased disk edema, partial resolution of the serous retinal detachment, and formation of a macular star exudate. Over the subsequent three weeks visual acuity improved in the left eye to 20/30, and the white inner retinal lesions resolved gradually. A focal retinal pigment epithelial disturbance developed at the site of the more severe lesions.

Initial laboratory findings included a normal chest x-ray and complete blood cell count, a nonreactive rapid plasma reagin, and normal or negative titers for toxoplasmosis, Epstein-Barr virus, cytomegalovirus, Lyme disease, histoplasmosis, blastomycosis, coccidioidomycosis, and aspergillosis. Westergren sedimentation rate was normal, but antinuclear antibody test-

ing was borderline positive at a 1:40 titer in a nucleolar pattern. Anti-DNA testing was negative. Although total hemolytic complement levels were normal, C1q-binding assay was borderline increased. A purified, protein-derivative tuberculin skin test was nonreactive, but *Candida* skin testing was reactive.

At a follow-up examination 23 months later, the patient had no visual complaints, visual acuity of 20/15 in both eyes, and a few small, faint chorioretinal scars that corresponded to some of the previous white lesions (Fig. 2) as well as a subtle macular retinal pigment epithelial disturbance in the left eye. Repeat antinuclear antibody and complement function tests were normal two years after the initial occurrence.

Case 2

A 37-year-old woman had sudden loss of vision in the right eye three days before examination. Two weeks before, she had developed a fever of 39.0 C with chills and general fatigue that resolved gradually in seven days without treatment. Her ocular and medical history showed varicella as a child. Initial ocular examination disclosed visual acuity of 20/20 in both eyes, a trace right relative afferent pupillary defect, and a dense centrocecal scotoma in the right eye on Goldmann visual field testing. Slit-lamp biomicroscopy disclosed a moderate bilateral posterior vitreous cellular reaction without anterior segment inflammation.

Ophthalmoscopy of the right eye showed a normal disk with a thin inferotemporal arteriole and an area of pale retina underlying this vessel, which measured approximately 2×1.5 disk diameters (Fig. 3). The disk and vessels appeared normal in the left eye. There were multiple, bilateral (three right eye, 11 left eye) inner retinal lesions, which were small (100 to 200 μm), yellow-white, round, and distributed in the posterior pole and midperipheral retina (Figs. 3 and 4). The stereoscopic fluorescein angiograms demonstrated an early blocking defect and delayed filling of vessels in the inferotemporal aspect of the papillomacular bundle in the right eye with faint, focal late hyperfluorescence along its nasal aspect, consistent with an occluded branch of the retinal artery (Fig. 3). The multiple white lesions seen during ophthalmoscopy were characterized by a central hypofluorescence with a faint hyperfluorescent rim during early phases of the angiogram (Fig. 3) and irregular central hypofluorescence with

a hyperfluorescent rim in the late phases of the angiogram (Figs. 3 and 4). Examination with a Goldmann contact lens confirmed the inner retinal location of these lesions.

The initial diagnosis was an occluded branch of the retinal artery of the right eye and bilateral, multifocal retinitis of unknown, although possible infectious cause. During the next four months, the white retinal lesions resolved gradually. Only a few of the more severe retinal lesions developed a focal retinal pigment epithelial disturbance (Figs. 3 and 4).

Initial laboratory findings included a normal chest x-ray and complete blood cell count, a nonreactive rapid plasma reagin, and normal or negative titers for Lyme disease, toxoplasmosis, histoplasmosis, blastomycosis, coccidioidomycosis, and aspergillosis. Varicella-zoster and Epstein-Barr virus titers were consistent with previous exposures. Herpes simplex IgM titers were borderline positive, although three IgG titers were negative over the next three months. Convalescent herpes simplex IgM titers were negative. Sedimentation rate, antinuclear antibody, and complement studies were normal.

Discussion

Acute multifocal inner retinitis involves primarily the inner retinal layers without initially affecting the deep retina or retinal pigment epithelium. The location and appearance, as well as the associated vitreitis and subsequent retinal pigment epithelial disturbance or chorioretinal scarring, differentiate acute multifocal inner retinitis from cotton-wool spots. It is unlikely that these inner retinal opacities were secondary to a multifocal choroidal process because several lesions progressed from an inner retinal location to a subtle retinal pigment epithelial disturbance or, in some instances, to a faint chorioretinal scar. Thus, the outer retina, retinal pigment epithelium, and choroid may become involved secondarily as the more intense lesions resolve.

Both cases of acute multifocal inner retinitis share other features. Each patient had a nonspecific prodrome of fever, chills, headaches, and general malaise and fatigue two to four weeks before the onset of the visual disturbance. An acute change in vision one to six days before examination had prompted the request for medical attention. Ophthalmic examination found

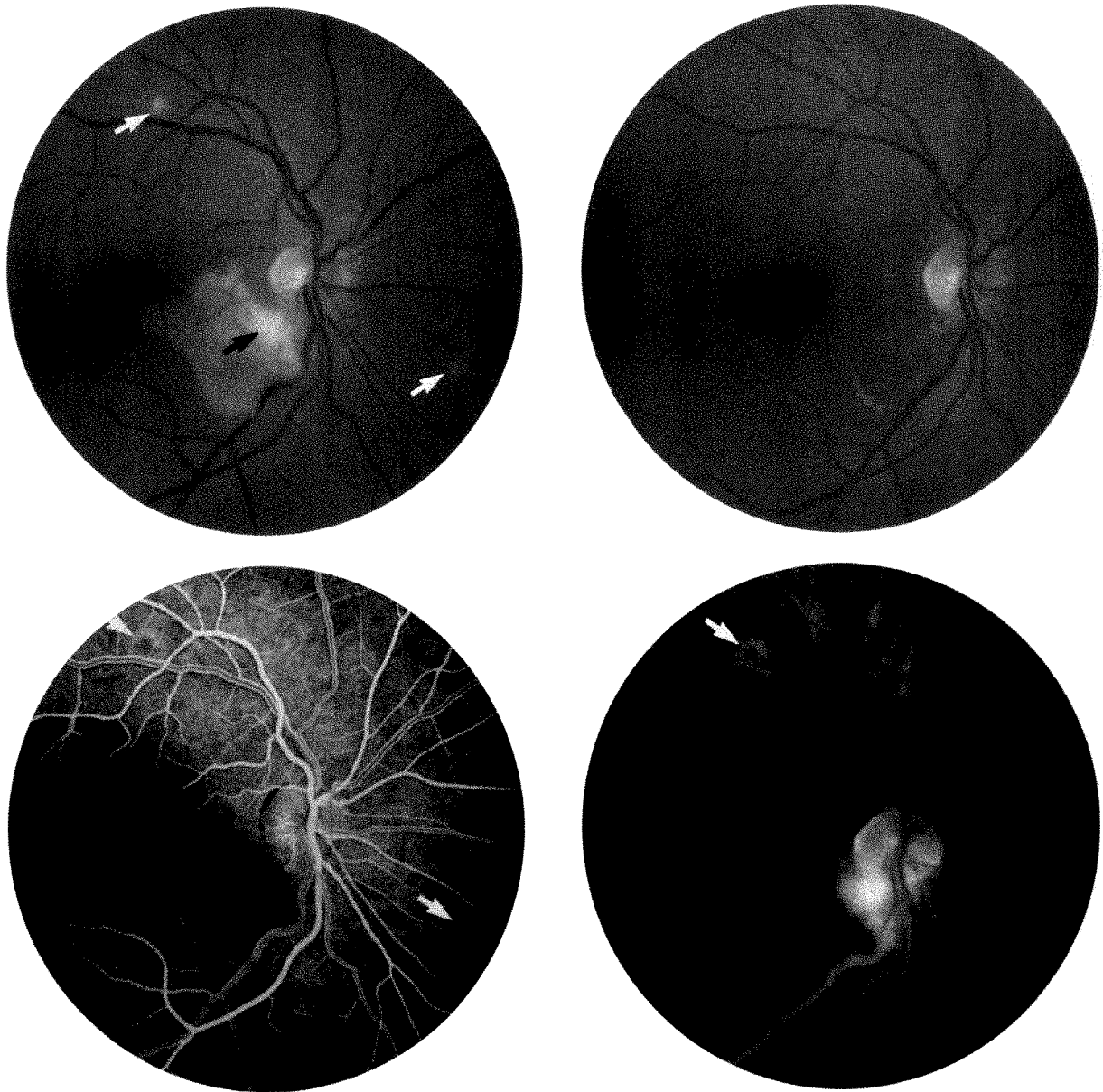


Fig. 3 (Foster and associates). Case 2, right eye. Top left, Focal area of retinal edema, secondary to an occluded branch of the retinal artery, which extends inferotemporally from the disk with an inner retinal lesion at the superonasal border of the retinal edema (black arrow). The retinal lesion overlies a small branch retinal artery. Two additional inner retinal lesions are also seen (white arrows). Top right, Nine weeks later the retinal edema has resolved, as has most of the overlying white inner retinal lesion inferotemporal to the disk. Bottom left, Early venous-phase fluorescein angiogram at initial manifestation showing central hypofluorescence (lower arrow) and irregular hyperfluorescent rim (upper arrow) corresponding to inner retinal lesions as well as blocking from the retinal edema secondary to the branch retinal artery occlusion. Bottom right, Late-phase angiogram showing leakage from retinal vessels and inner retinal lesion inferotemporally to the disk and marginal hyperfluorescence and central hypofluorescence above the superotemporal arcade corresponding to a small inner retinal lesion.

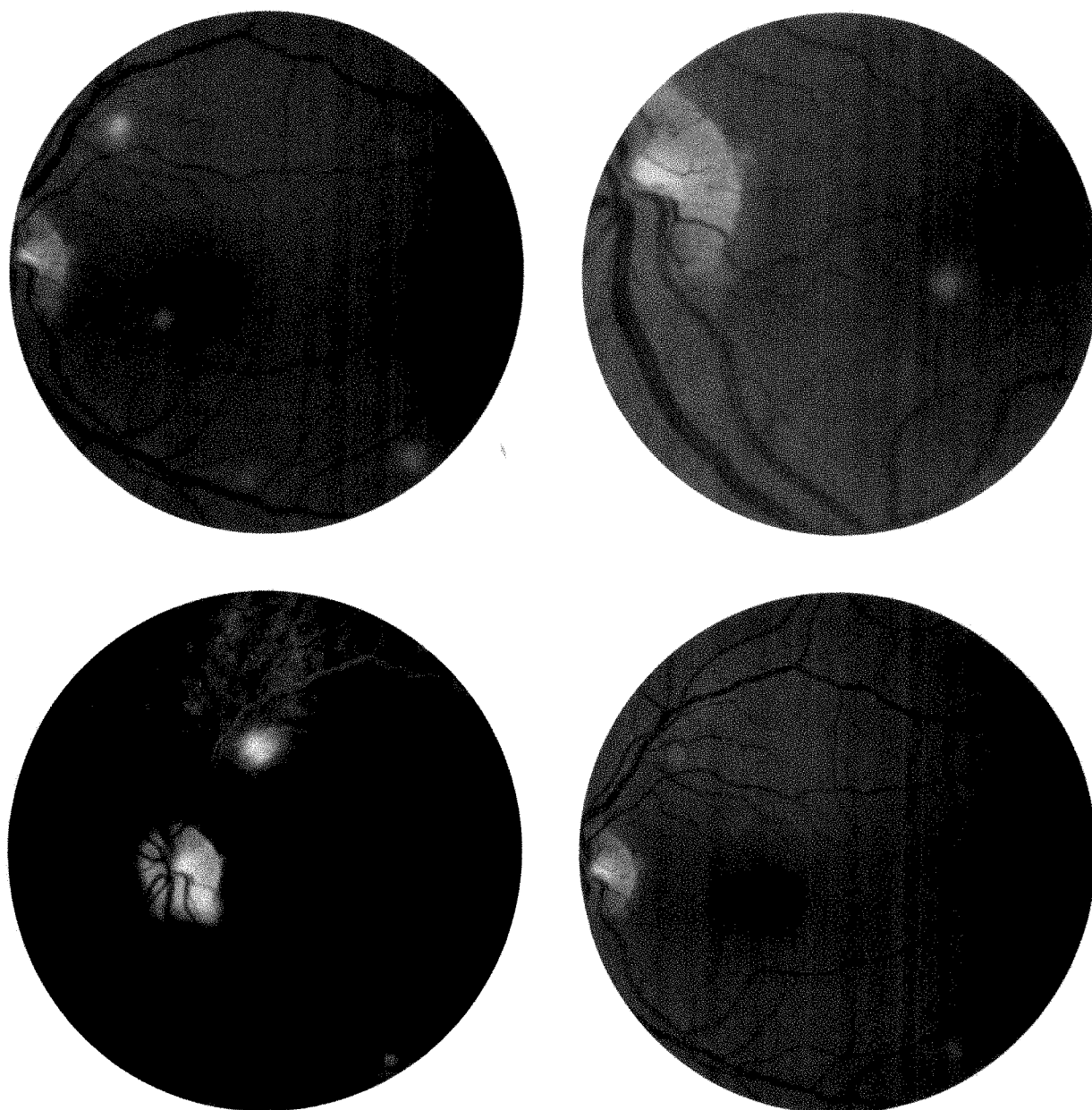


Fig. 4 (Foster and associates). Case 2, left eye. Top left, Multiple inner retinal lesions randomly distributed in posterior pole. Top right, Enlarged view of parafoveal inner retinal lesion. Note the loss of underlying vessel detail. Bottom left, Late-phase fluorescein angiogram showing focal hyperfluorescence corresponding to inner retinal lesions. Bottom right, Nine weeks after the initial occurrence a few faint chorioretinal scars correspond to sites of previous inflammation. Note that some of the opacities have resolved without visible sequelae.

mild vitreitis without anterior segment inflammation and multiple, bilateral lesions, which were small (100 to 200 μm), yellow-white, round, and confined to the inner retinal layers in the posterior pole and midperipheral retina. On the fluorescein angiogram, the inner retinal

lesions demonstrated early central hypofluorescence with a faint hyperfluorescent rim. Late phases showed irregular central hypofluorescence and increased marginal hyperfluorescence. Clinical examination with a Goldmann contact lens confirmed the inner retinal loca-

tion of these multifocal retinal opacities. Neither patient had additional findings on general physical examination or significantly abnormal laboratory results.

The differential diagnosis of acute multifocal inner retinitis includes a number of conditions, some of which are associated with infection. Retinal infiltrates after a viral syndrome were described by Goldstein and Pavan¹ in 1985. In ten eyes of six patients, they observed multifocal, predominantly deep, white retinal infiltrates distributed in the posterior pole and peripheral retina with minimal or no associated vitreitis.¹ Two patients had superficial and deep retinal lesions. Both patients lost some visual acuity because of disk edema, macular edema, or both. The authors did not attribute the decreased visual acuity to superficial retinal lesions. Two patients lost moderate degrees of visual acuity, one attributed to a parafoveal deep retinal lesion and the other to cystoid macular edema. As with our two patients, the more intense or deeper lesions developed variable amounts of retinal pigment epithelial disturbance and chorioretinal scarring. Fluorescein angiograms in one case disclosed early blocking and late staining of a retinal lesion.

Several authors have described bilateral, multifocal retinitis or chorioretinitis associated with Leber's idiopathic stellate neuroretinitis,²⁻⁴ which is commonly preceded by a self-limited upper respiratory or gastrointestinal illness. Most of these lesions were described as small (300 to 400 μm), round, white, and deep retinal in location. Inner retinal or superficial lesions have also been reported.² In most cases, fluorescein angiograms have shown focal late-phase hyperfluorescence corresponding to the retinal lesions, and several lesions have progressed to small chorioretinal scars or retinal pigment epithelial disturbances.

Multifocal retinitis with vitreitis associated with Epstein-Barr virus has been described, although the lesions were confined to the outer retina and retinal pigment epithelium.⁵ These lesions were significantly smaller (20 to 75 μm) than the lesions in acute multifocal inner retinitis and had an indistinct border with associated retinal pigment epithelial clumping and depigmentation. Fluorescein angiograms typically show early and late hyperfluorescence.

The multifocal choroiditis and panuveitis associated with Epstein-Barr virus can result in complications, such as subretinal fibrosis, disci-

form scarring, and choroidal neovascular membranes.⁶ In our cases, the Epstein-Barr virus titer was negative in the first patient and consistent with past exposure in the other, whereas the serologic findings during the acute phase were consistently positive in the previously reported cases.^{5,6}

Herpes simplex virus has also been associated with multifocal chorioretinitis involving the outer retina, retinal pigment epithelium, and choroid, with a mild anterior uveitis.⁷

Toxoplasmosis characteristically involves the inner retinal layer and can assume any of three morphologic configurations, including a punctate inner or outer retinitis.^{8,9} Both of our patients had negative toxoplasmosis titers and no chorioretinal scarring typical of previous toxoplasmosis chorioretinitis, although others have described multifocal toxoplasmic chorioretinitis without typical inactive scars.^{8,9}

A mild type of the acute retinal necrosis syndrome has been described with multifocal, midperipheral pale-yellow retinal lesions associated with vitreitis and anterior uveitis.¹⁰ The slowly progressive course and confluent spread of these lesions, subsequent chorioretinal degeneration, and anterior segment inflammation differentiate this syndrome from acute multifocal inner retinitis.

Multiple evanescent white-dot syndrome, described in 1984 by Jampol and associates,¹¹ is characterized by acute unilateral loss of vision and ophthalmoscopic findings of small (100 to 200 μm) white dots at the level of the retinal pigment epithelium or outer retina associated with vitreitis in young patients. Approximately half of the patients with this syndrome have had a preceding febrile illness. Additional findings in the white-dot syndrome include a characteristic fine macular granularity, retinal vascular sheathing, and a typically benign clinical course with regression of the lesions over a period of weeks. More recently, recurrent and bilateral cases¹² and complications such as subretinal neovascularization¹³ and possible optic nerve involvement¹⁴ have been described. This syndrome differs from acute multifocal inner retinitis; the white-dot syndrome is usually unilateral, and the lesions involve the outer retina and retinal pigment epithelium.

Presumed ocular histoplasmosis,¹⁵ multifocal choroiditis and panuveitis,¹⁶ punctate inner choroidopathy,¹⁷ acute posterior multifocal placoid pigment epitheliopathy,¹⁸ acute retinal

pigment epitheliitis,¹⁹ birdshot retinochoroidopathy,²⁰ recurrent multifocal choroiditis,²¹ and acute macular neuroretinopathy,²² although multifocal, do not resemble acute multifocal inner retinitis on the basis of location and appearance of the lesions, disease course, or associated complications.

The cause of most of these multifocal retinal, choroidal, or chorioretinal processes is presumed or unknown. Therefore, it becomes useful to classify them on the basis of their anatomic location and appearance, associated ocular findings, and the clinical course and complications. This descriptive classification is not without problems, however, because the causes are often unknown, the symptoms and signs overlap, and the complications and clinical outcomes vary.

Several authors have associated a self-limited antecedent illness with multifocal retinal lesions and have speculated that hematogenous spread could result in such a distribution.¹⁻⁴ The mechanism of multifocal inner retinitis is unclear, although there is probably a spectrum of retinal and choroidal responses to infectious agents. For example, it is possible that acute multifocal inner retinitis and multiple evanescent white-dot syndrome are similar postinfectious processes. Clinically, acute multifocal inner retinitis involves the inner retina; multiple evanescent white-dot syndrome involves the retinal pigment epithelium and outer retina. The different lesion location may reflect which circulation, retinal or choroidal, is involved predominantly.

Viral inclusions in vascular endothelial cells²³ and autoantibodies to vascular endothelial cell antigens²⁴ have been found, and a virus, viral antigen, or postinfectious antigen-antibody complex could have been deposited in either the retinal or choroidal vascular endothelium, contributing to either an inner retinal lesion, retinal pigment epithelial lesion, or a choroidal lesion.

The incidence of multifocal retinal and choroidal lesions after an illness, including acute multifocal inner retinitis, may be higher than expected, because most of the patients likely have no ocular symptoms. Additionally, complications such as neuroretinitis, serous retinal detachment, or a vascular occlusion are probably the exception to the natural course of this disorder. Ultimately, defining the epidemiologic characteristics of acute multifocal inner reti-

nititis and other postinfectious multifocal retinal and choroidal processes requires a large prospective study involving patients with recent nonspecific febrile or viral illnesses.

References

1. Goldstein, B. G., and Pavan, P. R.: Retinal infiltrates in six patients with an associated viral syndrome. *Retina* 5:144, 1985.
2. Carroll, D. M., and Franklin, R. M.: Leber's idiopathic stellate retinopathy. *Am. J. Ophthalmol.* 93:96, 1982.
3. Dreyer, R. F., Hopen, G., Gass, J. D. M., and Smith, J. L.: Leber's idiopathic stellate neuroretinitis. *Arch. Ophthalmol.* 102:1140, 1984.
4. Maitland, C. G., and Miller, N. R.: Neuroretinitis. *Arch. Ophthalmol.* 102:1146, 1984.
5. Raymond, L. A., Wilson, C. A., Linnemann, C. C., Jr., Ward, M. A., Bernstein, D. I., and Love, D. C.: Punctate outer retinitis in acute Epstein-Barr virus infection. *Am. J. Ophthalmol.* 104:424, 1987.
6. Tiedeman, J. S.: Epstein-Barr viral antibodies in multifocal choroiditis and panuveitis. *Am. J. Ophthalmol.* 103:659, 1987.
7. Grutzmacher, R. D., Henderson, D., McDonald, P. J., and Coster, D. J.: Herpes simplex chorioretinitis in a healthy adult. *Am. J. Ophthalmol.* 96:788, 1983.
8. Friedmann, C. T., and Knox, D. L.: Variations in recurrent active toxoplasmic retinochoroiditis. *Arch. Ophthalmol.* 81:481, 1969.
9. Doft, B. H., and Gass, J. D. M.: Punctate outer retinal toxoplasmosis. *Arch. Ophthalmol.* 103:1332, 1985.
10. Matsuo, T., Nakayama, T., Koyama, T., Koyama, M., and Matsuo, N.: A proposed mild type of acute retinal necrosis syndrome. *Am. J. Ophthalmol.* 105:579, 1988.
11. Jampol, L. M., Sieving, P. A., Pugh, D., Fishman, G. A., and Gilbert, H.: Multiple evanescent white-dot syndrome. *Arch. Ophthalmol.* 102:671, 1984.
12. Aaberg, T. M., Campo, R. V., and Joffe, L.: Recurrences and bilaterality in the multiple evanescent white-dot syndrome. *Am. J. Ophthalmol.* 100:29, 1985.
13. Wyhinny, G. J., Jackson, J. L., Jampol, L. M., and Caro, N. C.: Subretinal neovascularization following multiple evanescent white-dot syndrome. *Arch. Ophthalmol.* 108:1384, 1990.
14. Dodwell, D. G., Jampol, L. M., Rosenberg, M., Berman, A., and Zaret, C. R.: Optic nerve involvement associated with the multiple evanescent white-dot syndrome. *Ophthalmology* 97:862, 1990.
15. Watzke, R. C., and Claussen, R. W.: The long-

term course of multifocal choroiditis (presumed ocular histoplasmosis). *Am. J. Ophthalmol.* 91:750, 1981.

16. Dreyer, R. F., and Gass, J. D. M.: Multifocal choroiditis and panuveitis. A syndrome that mimics ocular histoplasmosis. *Arch. Ophthalmol.* 102:1776, 1984.

17. Watzke, R. C., Packer, A. J., Folk, J. C., Benson, W. E., Burgess, D., and Ober, R. R.: Punctate inner choroidopathy. *Am. J. Ophthalmol.* 98:572, 1984.

18. Gass, J. D. M.: Acute posterior multifocal placoid pigment epitheliopathy. *Arch. Ophthalmol.* 80:177, 1968.

19. Krill, A. E., and Deutman, A. F.: Acute retinal pigment epitheliitis. *Am. J. Ophthalmol.* 74:193, 1972.

20. Ryan, S. J., and Maumenee, A. E.: Birdshot retinochoroidopathy. *Am. J. Ophthalmol.* 89:31, 1980.

21. Morgan, C. M., and Schatz, H.: Recurrent multifocal choroiditis. *Ophthalmology* 93:1138, 1986.

22. Bos, P. J. M., and Deutman, A. F.: Acute macular neuroretinopathy. *Am. J. Ophthalmol.* 80:573, 1975.

23. Bulpitt, K. J., and Brahn, E.: Systemic lupus erythematosus and concurrent cytomegalovirus vasculitis. Diagnosis by antemortem skin biopsy. *J. Rheumatol.* 16:677, 1989.

24. Brasile, L., Dremer, J. M., Clarke, J. L., and Cerilli, J.: Identification of an autoantibody to vascular endothelial cell-specific antigens in patients with systemic vasculitis. *Am. J. Med.* 87:74, 1989.

OPHTHALMIC MINIATURE

In memory of this accident, Lycurgus built a temple to Minerva, sur-named Optilētis; *optilus* being the Doric of these parts for *ophthalmus*, the eye. Some authors, however, of whom Dioscorides is one (who wrote a treatise on the commonwealth of Sparta), say that he was wounded, indeed, but did not lose his eye with the blow; and that he built the temple in gratitude for the cure. Be this as it will, certain it is, that, after this misadventure, the Lacedæmonians made it a rule never to carry so much as a staff into their public assemblies.

Plutarch, *The Lives of the Noble Grecians and Romans*
Chicago, Encyclopaedia Britannica, 1952, p. 37

Unilateral Frosted Branch Angiitis

Stephanie L. Sugin, M.D., Dale E. Henderly, M.D., Scott M. Friedman, M.D.,
Lee M. Jampol, M.D., and J. William Doyle, M.D.

We examined two patients with monocular frosted branch angiitis. The patients were young and healthy; they rapidly developed severe visual loss with thick, white sheathing of the retinal veins and responded promptly to systemic corticosteroids. The fluorescein angiograms showed late leakage from the retinal veins, without evidence of stasis or occlusion. Frosted branch angiitis can be either a unilateral or a bilateral condition. We believe the potential for visual loss and the prompt response to systemic corticosteroids make early, accurate diagnosis and institution of therapy desirable.

IN 1976, Ito and associates¹ described a 6-year-old boy who had sudden bilateral visual loss and unusual thick sheathing of the retinal vessels. They called this condition frosted branch angiitis. Since then, eight similar cases have been reported,¹⁻⁶ all of which have been bilateral. We treated two patients with unilateral frosted branch angiitis.

Case Reports

Case 1

A 32-year-old man had acute visual loss in the right eye on Dec. 16, 1988. His ocular history was unremarkable. He had been admitted to the hospital five weeks previously for a presumed severe viral syndrome. At the time of his illness, he had fever and a transiently in-

creased white blood cell count to 20,000 cells/mm³ with 80% polymorphonuclear leukocytes. Laboratory evaluation included an erythrocyte sedimentation rate of 30 mm/hr, a hemoglobin level of 15.8 g/dl, a hematocrit level of 44.8%, and normal results of sequential multiple analyzer-20, prothrombin time, partial thromboplastin time, urinalysis, and complement levels. Additionally, he had negative test results for antinuclear antibody, rheumatoid factor, blood cultures, chest x-ray, sinus films, computed tomography of the abdomen, and gallium scan. The patient had an increased C-reactive protein, an Epstein-Barr virus IgG titer of 1:320, and a negative Epstein-Barr virus IgM titer. The symptoms and leukocytosis improved spontaneously. Four weeks later he developed acute visual loss in his right eye.

Ocular examination one day after onset of his visual loss disclosed best-corrected visual acuity of R.E.: counting fingers and L.E.: 20/20. External examination disclosed a moderate afferent pupillary defect in the right eye. Biomicroscopy of the anterior segment of the right eye showed a quiet anterior chamber and mild vitreous cells. Ophthalmoscopy of the right eye showed extensive thick, white, confluent sheathing of the retinal veins, blurring of the disk margins, extensive intraretinal and preretinal hemorrhage, and a serous macular detachment (Fig. 1). The left eye showed no abnormalities. Fluorescein angiography of the right eye demonstrated leakage of dye from the veins. There was no evidence of vascular occlusion (Fig. 2). Laboratory values for complete blood cell count, antinuclear antibody, rheumatoid factor, human immunodeficiency virus, sequential multiple analyzer-20, and fluorescent treponemal antibody absorption test were normal. Viral and *Toxoplasma* titers were negative, except for an Epstein-Barr virus IgG titer of 1:512, compared to an Epstein-Barr virus IgG titer of 1:320 on Nov. 8, 1988. Epstein-Barr virus IgM titers were negative.

The patient was given 80 mg of prednisone daily, and within two weeks visual acuity had improved to 20/200, and the marked sheathing

Accepted for publication Feb. 20, 1991.

From the Departments of Ophthalmology, Northwestern University, Chicago, Illinois (Drs. Sugin, Henderly, and Jampol) and University of Florida, Gainesville, Florida (Drs. Friedman and Doyle). This study was supported in part by an unrestricted grant from Research to Prevent Blindness, Inc.

Reprint requests to Dale E. Henderly, M.D., Northwestern University, Department of Ophthalmology, 303 E. Chicago Ave., Ward Bldg., 4th Fl., Chicago, IL 60611.

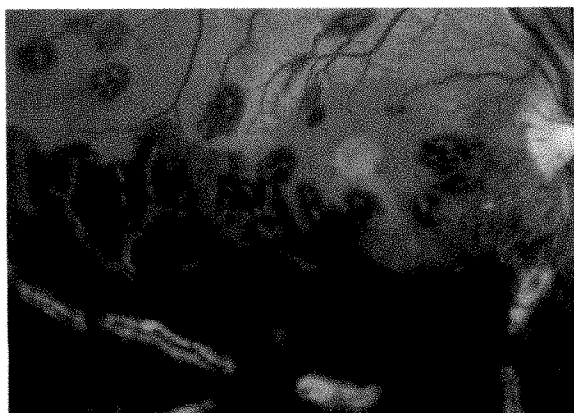


Fig. 1 (Sugin and associates). Case 1. Right eye with extensive venous sheathing, hemorrhage, and a serous macular detachment.



Fig. 2 (Sugin and associates). Case 1. Fluorescein angiogram of the right eye demonstrating late leakage of dye from the veins.

of the vessel walls had almost disappeared. Within two months visual acuity had returned to 20/20-. The prednisone was gradually tapered, and the phlebitis has not recurred.

Case 2

A 26-year-old man had a five-day history of gradually decreasing vision in his right eye on May 26, 1989. The patient's medical and ocular history were unremarkable. Before this examination, he had been treated by his local physician with hydrocortisone acetate for a presumed viral conjunctivitis.

Examination disclosed best-corrected visual acuity of R.E.: counting fingers and L.E.: 20/20. The right eye showed conjunctival chemosis with minimal injection. Biomicroscopy of the right eye disclosed mild cell and moderate flare in the anterior chamber and moderate cells in the vitreous. The lens was clear. Results of slit-lamp examination of the left eye were normal. Ophthalmoscopy of the right eye showed disk swelling and enlarged tortuous veins with dense perivenous sheathing. Intraretinal hemorrhages were scattered throughout the posterior pole. The macula had an exudative detachment (Fig. 3). The left fundus was normal.

Laboratory studies disclosed an erythrocyte sedimentation rate of 4 mm/hr. The white blood cell count was 7,400 cells/mm³ with a normal differential. Results of liver function tests were normal, with the exception of a mildly increased serum glutamic pyruvic transaminase level of 52 IU/l (normal, 0 to 40 IU/l). Tests for HIV, hepatitis A and B, rheumatoid factor, antinuclear antibody, and VDRL were nonreactive. Results of a Lyme titer were nega-

tive, and the patient had a normal chest x-ray. Fluorescein angiography disclosed diffuse leakage of dye from the veins without any impairment of flow (Fig. 4).

The patient was given 80 mg of oral prednisone daily. He also received topical prednisolone acetate and atropine 1% twice daily to the right eye. Over the next month, visual acuity gradually improved to 20/80. Ophthalmoscopy at that time showed a marked improvement in the perivascular sheathing and resolution of the macular detachment. Star-shaped macular exudates with a small area of scarring in the macula accounted for the decreased visual acuity. The oral corticosteroids were tapered, and the condition has not recurred.

Discussion

Frosted branch angiitis manifests with acute visual loss in an otherwise healthy patient. The fundus findings are dramatic and characterized by severe white sheathing of the retinal veins. A variable amount of anterior chamber and vitreous inflammation also occurs. Fluorescein angiography demonstrates leakage of dye from the veins but no evidence of stasis or occlusion. The clinical findings respond dramatically to systemic corticosteroids, and no recurrences have been reported in the previously described patients.

Our two patients are similar to the previously reported cases of frosted branch angiitis; they had rapid onset of visual loss, severe sheathing

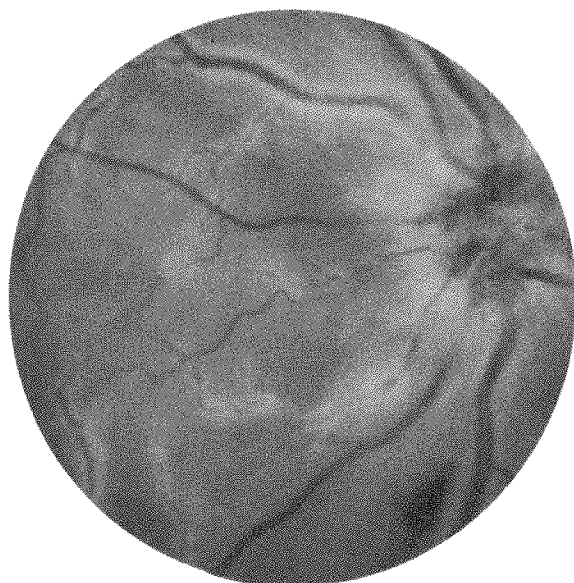


Fig. 3 (Sugin and associates). Case 2. Right eye with disk swelling and dense perivenous sheathing.

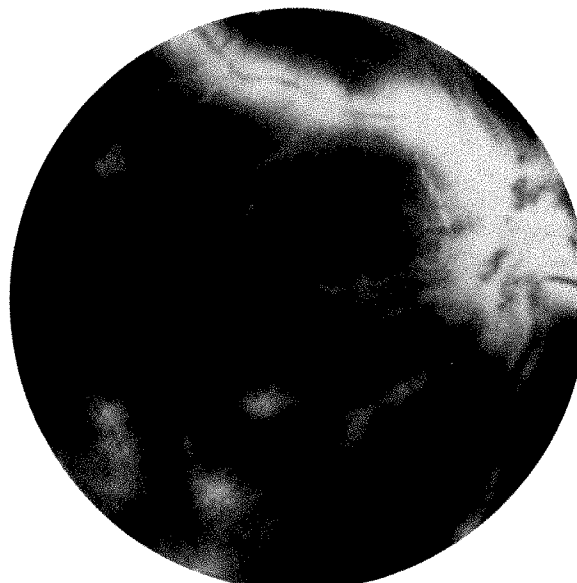


Fig. 4 (Sugin and associates). Case 2. Fluorescein angiogram of the right eye with diffuse leakage of dye from the veins without any impairment of flow.

of the retinal veins, prompt response to systemic corticosteroids, and no recurrences. The fluorescein angiograms showed late leakage from the retinal veins with no evidence of stasis or occlusion. Additionally, both of our patients developed optic disk swelling and serous macular detachments, which have been previously described in this disease.⁶ The macular scar that accounted for our second patient's final visual acuity of 20/80 is also similar to previously described patients.⁶

Although early articles described frosted branch angiitis as a type of vasculitis affecting both arteries and veins,^{1,3} more precise descriptions of this condition have led to the conclusion that frosted branch angiitis is a severe periphlebitis.^{5,6} Retinal periphlebitis may be seen with many other ocular and systemic inflammatory diseases, including sarcoidosis,^{7,8} syphilis,⁹ tuberculosis,¹⁰ multiple sclerosis,^{11,12} HIV infection,¹³ and acquired diseases of connective tissue.¹⁴ Neither of our patients had any clinical or laboratory findings to support these diagnoses.

The cause of frosted branch angiitis remains unknown. Viral diseases, particularly those caused by the herpesvirus, have been associated with prominent retinal vasculitis, usually with concurrent retinitis.¹⁵⁻¹⁷ One patient (Case 1) had isolated increased IgG titers to Epstein-Barr virus, and some of the previously described patients have had positive viral titers to

both herpes simplex and herpes zoster.⁶ A viral trigger for this condition is suggested by the clinical setting, the acute onset of the disease, and the variable preceding flulike illness. The clinical findings of frosted branch angiitis may not represent a direct viral infection of the retinal veins but may be secondary to an immune-mediated process. Immune complex deposition in the vessels might explain the striking clinical course. The dramatic response to corticosteroids supports this hypothesis.

The findings in our patients demonstrate that frosted branch angiitis may occur unilaterally as well as bilaterally. Although the natural progression of the disease without corticosteroids is not well delineated, the possibility for permanent loss of visual acuity secondary to macular scarring exists. Therefore, we believe the dramatic and apparently permanent resolution of the vasculitis after instituting systemic corticosteroids makes early, accurate diagnosis and institution of corticosteroids imperative.

References

1. Ito, Y., Nakano, M., Kyo, N., and Takeuchi, M.: Frosted branch angiitis in a child. *Jpn. J. Clin. Ophthalmol.* 30:797, 1976.

2. Sakanishi, Y., Kanagami, S., and Ohara, K.: Frosted retinal angiitis in children. *Jpn. J. Clin. Ophthalmol.* 38:803, 1984.
3. Yamane, S., Nishiuchi, T., Nakagawa, Y., Iwase, T., and Hama, M.: A case of frosted branch angiitis of the retina. *Folia Ophthalmol. Jpn.* 36:1822, 1985.
4. Higuchi, K., Maeda, K., Uji, T., and Yokoyama, M.: A case of acute infantile uveitis with frosted branch angiitis. *Jpn. Rev. Clin. Ophthalmol.* 79:2660, 1985.
5. Watanabe, Y., Takeda, N., and Adachi Usami, E.: A case of frosted branch angiitis. *Br. J. Ophthalmol.* 71:553, 1987.
6. Kleiner, R. C., Kaplan, H. J., Shakin, J. L., Yannuzzi, L. A., Croswell, H. H., Jr., and McLean, W. C., Jr.: Acute frosted retinal periphlebitis. *Am. J. Ophthalmol.* 106:27, 1988.
7. Sanders, M. D., and Shilling, J. S.: Retinal, choroidal and optic disc involvement in sarcoidosis. *Trans. Ophthalmol. Soc. U.K.* 96:140, 1976.
8. Gould, H., and Kaufman, H.: Sarcoid of the fundus. *Arch. Ophthalmol.* 65:161, 1961.
9. Mendelsohn, A. D., and Jampol, L. M.: Syphilitic retinitis. A cause of necrotizing retinitis. *Retina* 4:221, 1984.
10. Fountain, J. A., and Werner, R. B.: Tuberculous retinal vasculitis. *Retina* 4:48, 1984.
11. Rucker, C. W.: Sheathing of the retinal veins in multiple sclerosis. *Mayo Clin. Proc.* 47:335, 1973.
12. Arnold, A. C., Pepose, J. S., Hepler, R. S., and Foos, R. Y.: Retinal periphlebitis and retinitis in multiple sclerosis. *Ophthalmology* 91:255, 1984.
13. Kestelyn, P., Lepage, P., and Van de Perre, P.: Perivasculitis of the retinal vessels as an important sign in children with AIDS-related complex. *Am. J. Ophthalmol.* 100:614, 1985.
14. Sanders, M. D., and Graham, E. M.: Retinal vasculitis. *Postgrad. Med. J.* 64:488, 1966.
15. Ostier, M. D., and Thygeson, P.: The ocular manifestations of herpes zoster, varicella, infectious mononucleosis, and cytomegalovirus disease. *Surv. Ophthalmol.* 21:148, 1976.
16. Fisher, J. P., Lewis, M. L., Blumenkranz, M., Culbertson, W. W., Flynn, H. W., Jr., Clarkson, J. G., Gass, J. D. M., and Norton, E. W. D.: The acute retinal necrosis syndrome. Part I. Clinical manifestations. *Ophthalmology* 89:1309, 1982.
17. Uninsky, E., Jampol, L. M., Kaufman, S., and Naraqi, S.: Disseminated herpes simplex infection with retinitis in a renal allograft recipient. *Ophthalmology* 90:175, 1983.

An In Vitro Study of the Potency and Stability of Fortified Ophthalmic Antibiotic Preparations

Brian E. Bowe, M.D., James W. Snyder, Ph.D., and Richard A. Eiferman, M.D.

We studied the potency of fortified ophthalmic antibiotic preparations of cefazolin sodium (50 mg/ml) and tobramycin sulfate (15 mg/ml), as measured by the minimum inhibitory concentration, against *Streptococcus pneumoniae* and *Pseudomonas aeruginosa*, respectively. We also examined absorbance spectra, pH, and the effect of storage temperature on these fortified solutions to determine their stability over a four-week period. Cefazolin and tobramycin maintained a constant potency throughout the experiment. There was no difference in potency if the fortified solutions were stored at 4 C or 24 C. Cefazolin stored at 24 C exhibited changes in both its absorbance spectra and pH after seven days. Cefazolin stored at 4 C and tobramycin stored at 24 C and 4 C remained stable throughout the four-week period.

FORTIFIED PREPARATIONS of ophthalmic antibiotics are often prescribed for the treatment of severe ocular infectious disease. These medications are usually prepared by combining standard parenteral or lyophilized antibiotic preparations with compatible vehicles that will not precipitate out the antibiotic at fortified concentrations.¹ Previously published work on older antibiotics has shown fortified solutions to be stable up to seven days.² With newer antibiotics, no data exist for fortified ophthalmic solutions, and their stability must be extrapolated from data on parenteral preparations or by comparison with similar antibiotics that have been previously studied.^{2,3} Our experience

with data from parenteral preparations is that they be discarded one week after preparation.

Since considerable time and expense are involved in formulating these drugs, we tested two commonly used antibiotics, cefazolin sodium and tobramycin sulfate, for this study. We examined the potency of these fortified solutions by measuring the minimum inhibitory concentration against common ophthalmic pathogens over a four-week period. We also tested the effect of storage temperature on potency and the stability of these solutions as measured by pH and absorbance spectra.

Material and Methods

A stock solution of cefazolin sodium was prepared by reconstituting the lyophilized powder with a methylcellulose artificial tear vehicle to a concentration of 50 mg/ml.

A stock solution of tobramycin sulfate was prepared by diluting a vial of the drug for intravenous use (40 mg/ml) with the methylcellulose artificial tear vehicle to a concentration of 15 mg/ml.

Each stock solution was divided in half and placed into standard ophthalmic dispensing bottles. One set of solutions was stored at room temperature (24 C) and the other set was refrigerated (4 C) for the duration of the experiment. All antibiotic solutions were stored in the dark.

Standard quality control reference strains of *Streptococcus pneumoniae* and *Pseudomonas aeruginosa* with known sensitivity to cefazolin and tobramycin, respectively, were chosen for the study. The bacteria were transferred daily to ensure purity and good growth.

On each test day, a bacterial suspension equal to the 0.5 McFarland turbidity standard was prepared in Mueller-Hinton broth. All antibiotic solutions were further diluted to a concentration of 1.0 mg/ml before serial dilutions with Mueller-Hinton broth were performed. For each dilution tube, 1.0 ml each of the bacterial

Accepted for publication March 27, 1991.

From the Department of Ophthalmology and Visual Sciences, University of Louisville (Drs. Bowe, Snyder, and Eiferman), and Veterans Administration Medical Center (Drs. Snyder and Eiferman), Louisville, Kentucky.

Reprint requests to Richard A. Eiferman, M.D., 301 E. Muhammed Ali Blvd., Louisville, KY 40202.

suspension and the antimicrobial agent were incubated together at 35 C in an aerobic environment for 24 hours.

The minimum inhibitory concentration is defined as the lowest concentration of antibiotic that yields no growth in the Mueller-Hinton broth.

An aliquot was taken from each stock solution and the pH measured with a laboratory micro pH meter.

Aliquots from the stock solutions were scanned with a spectrophotometer. All solutions were diluted with distilled water to give an absorbance reading less than 1.00. Absorbance was measured by using prominent peaks at 269 nm for tobramycin and at 272 nm for cefazolin. The artificial tear vehicle was prepared in an identical manner as the sample and its absorbance was measured at the sample peaks as a control.

The paired Student's *t*-test was used to detect significant differences between experimental groups and also within an experimental group over the course of an experiment.

Results

In the potency studies, cefazolin and tobramycin exhibited no loss of potency during the entire four-week period (Figs. 1 and 2). The storage temperature had no effect on the potency of either antibiotic. The artificial tear vehicle was unable to suppress bacterial growth at any of the serial dilution concentrations for each

organism and temperature tested. All stock solutions remained sterile throughout the duration of the study.

Cefazolin underwent a small but significant ($P = .05$) decrease in the absorption at 272 nm from Day 10 onward within the 24 C experimental group. The cefazolin 4 C group had stable absorbance spectra throughout the course of the experiment (Fig. 3). A comparison of the two experimental temperature groups showed a statistically significant difference appearing at Day 7 ($P = .05$) and thereafter ($P = .005$). Tobramycin did not exhibit any difference in absorbance spectra both within and between experimental groups for the duration of the experiment (Fig. 4). The artificial tear vehicle had no absorbance at the experimental wavelengths throughout the experiment.

In our pH studies, cefazolin underwent a slow, steady increase in the pH from Day 7 onward within the 24 C experimental group. The cefazolin 4 C group maintained a relatively constant pH for the duration of the experiment (Fig. 5). Tobramycin stored at 24 C underwent a mild initial drop in the pH before leveling out at Day 14 and then remained at that level for the duration of the experiment. Tobramycin at 4 C maintained a relatively constant pH for the duration of the experiment (Fig. 6).

Discussion

Fortified ophthalmic antibiotic preparations of cefazolin and tobramycin are commonly used

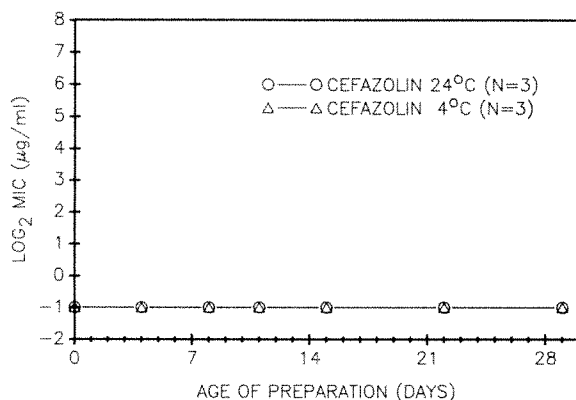


Fig. 1 (Bowe, Snyder, and Eiferman). The potency of fortified cefazolin solutions, as measured by minimum inhibitory concentration, over time.

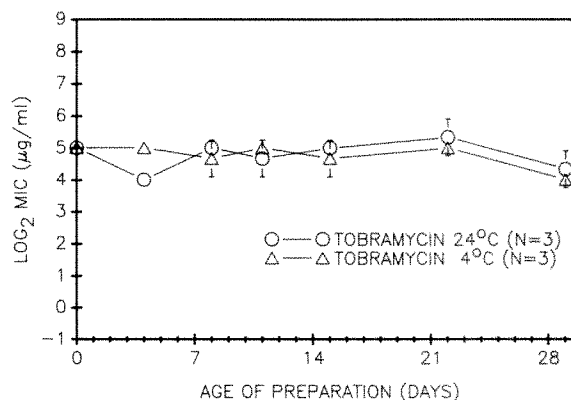


Fig. 2 (Bowe, Snyder, and Eiferman). The potency of fortified tobramycin solutions, as measured by minimum inhibitory concentration, over time.

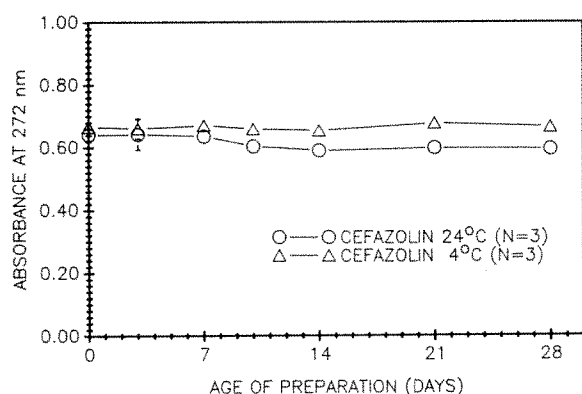


Fig. 3 (Bowe, Snyder, and Eiferman). The absorbance of fortified cefazolin solutions (50 mg/ml), measured at 272 nm, over time.

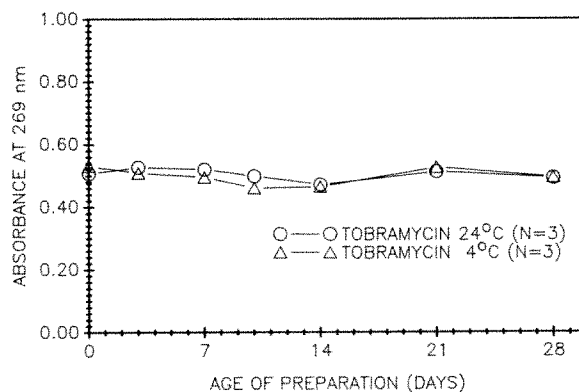


Fig. 4 (Bowe, Snyder, and Eiferman). The absorbance of fortified tobramycin solutions (15 mg/ml), measured at 269 nm, over time.

today, for the treatment of severe ocular infectious disease. Earlier work has shown that most antibiotics in artificial tear solutions demonstrate no significant loss of antibiotic activity at room temperature for seven days.² Newer antibiotics are continually being used as the first line of defense in microbial infections as resistance to the older antibiotics develops. Almost all of the current knowledge of the behavior of cefazolin and tobramycin as fortified solutions comes from extrapolation from data on parenteral preparations or by comparison with similar antibiotics that have been previously studied.^{2,3} It has been our experience that these fortified solutions come from the pharmacy with a recommendation that they be discarded after one week.

Our results show that the potency of cefazolin and tobramycin, as measured by minimum inhibitory concentration, remains at a clinically effective level for at least four weeks after they are prepared from standard parenteral preparations.

The physical properties can give important information on the stability of a medication in solution. Chemical keratitis, oxidation of a compound, precipitation and administration of an incorrect or nontherapeutic dose, and loss of potency are all sequelae of changes in physical properties of ophthalmic solutions. We also examined the effects of storage temperature on the pH and absorbance spectra of cefazolin and tobramycin at the two temperatures most readily available to patients, room temperature (24

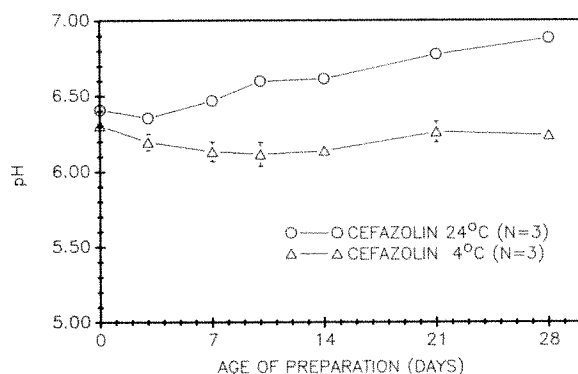


Fig. 5 (Bowe, Snyder, and Eiferman). The pH of fortified cefazolin solutions (50 mg/ml at 1:2,000 dilution) over time.

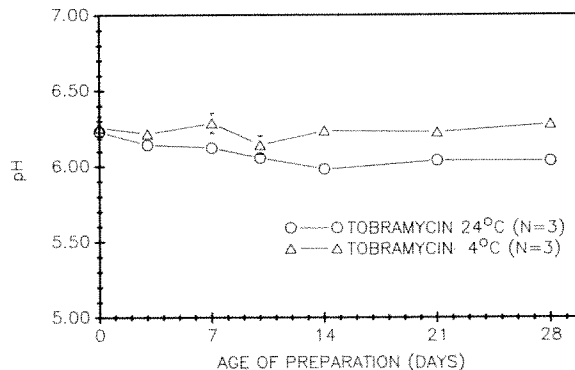


Fig. 6 (Bowe, Snyder, and Eiferman). The pH of fortified tobramycin solutions (15 mg/ml at 1:50 dilution) over time.

C) and under refrigeration (4 C). We found that although the storage temperature had no effect on the potency of either antibiotic, cefazolin underwent changes in its physical properties (absorbance spectra and pH) after seven to ten days when it is stored at 24 C. The nature of these changes is beyond the scope of this study but would seem to involve microbiologically active products as the potency of the solution remains constant.

Cefazolin stored at 4 C remained stable as did tobramycin at either of the storage temperatures for the entire four-week test period.

We recommend that fortified cefazolin should be kept under refrigeration, whereas fortified tobramycin may be kept at either room temperature (24 C) or under refrigeration (4 C). Both

preparations appear to be stable for at least one month after preparation and do not have to be discarded after one week, thus reducing replacement cost.

References

1. Baum, J. L.: Antibiotic mechanisms. In Smolin, G., and Thoft, R. A. (eds.): *The Cornea. Scientific Foundations and Clinical Practice*, ed. 1. Boston, Little, Brown, 1983, pp. 134-143.
2. Osborn, E., Baum, J. L., Ernst, C., and Koch, P.: The stability of ten antibiotics in artificial tear solutions. *Am. J. Ophthalmol.* 82:775, 1976.
3. McEvoy, G. K. (ed.): *AHFS Drug Information*. Bethesda, American Society of Hospital Pharmacies, 1990, pp. 66-67; 158-162.

OPHTHALMIC MINIATURE

Somewhere between retina and object, between vision and view, his eyes draw back, hesitate, and hover. At some fixed point in time and space he senses that he need not waste the effort of a glance. He does not see her, because for him there is nothing to see. How can a fifty-two-year-old white immigrant storekeeper with the taste of potatoes and beer in his mouth, his mind honed on the doe-eyed Virgin Mary, his sensibilities blunted by a permanent awareness of loss, see a little black girl? Nothing in his life even suggested that the feat was possible, not to say desirable or necessary.

Toni Morrison, *The Bluest Eye*
New York, Simon & Schuster, 1972, p. 42-43

Conjunctival Necrosis After Administration of Topical Fortified Aminoglycosides

C. R. Davison, F.R.C.S., S. J. Tuft, F.R.A.C.S., and J. K. G. Dart, F.R.C.S.

We treated 11 episodes of bulbar conjunctival necrosis that occurred in ten patients after therapy for suppurative keratitis with topical fortified aminoglycosides. Chemosis and mucous discharge preceded the development of an area of conjunctival pallor, which stained with fluorescein and was 5 to 10 mm from the corneoscleral limbus. Typical lesions developed in the inferior bulbar conjunctiva after a mean of 4.8 days and 112 mg of gentamicin sulfate (109 drops). The fortified aminoglycoside was the only agent common to all cases. The conjunctival defects healed completely between five and 13 days after treatment was modified to reduce or eliminate aminoglycoside exposure.

THE AMINOGLYCOSIDES are bactericidal antibiotics that prevent bacterial protein synthesis by irreversibly disrupting ribosomal function. They are used frequently in ophthalmic practice for the treatment of infections of the eye and ocular adnexa because their spectrum of activity includes many of the gram-negative enterobacteria and staphylococci.^{1,2} Gentamicin sulfate and tobramycin are effective against a wide range of organisms, including *Pseudomonas aeruginosa*, and are therefore a treatment of first choice in the management of suspected gram-negative bacterial keratitis.¹⁻⁸ They are usually formulated in a 0.3-g/100-ml (0.3%) concentration for antibacterial prophylaxis and for the treatment of minor external ocular infections, but a fortified strength (1.5%) is recommended for corneal infections when a bactericidal tissue concentration is essential.⁹

Topical aminoglycosides can be toxic to both

the corneal and conjunctival epithelium. Corneal toxicity is characterized by superficial punctate keratitis, delayed re-epithelialization, and corneal ulceration^{1,10-13}; conjunctival toxicity may produce hyperemia, chemosis, and punctate epithelial staining.² Nauheim, Nauheim, and Merrick¹⁴ described six patients with conjunctival defects caused by aminoglycosides. We treated ten patients who developed conjunctival necrosis while receiving treatment with fortified topical aminoglycosides.

Patients and Methods

Between June 1987 and May 1990, we treated ten patients who developed conjunctival necrosis during treatment with fortified topical aminoglycosides. We estimate that during this period approximately 180 patients with severe suppurative keratitis were admitted to our institution for treatment, and an additional 550 patients were treated as outpatients. Most of these patients received topical fortified aminoglycosides; therefore, the 11 episodes in 730 patients represent a 1% to 2% incidence of conjunctival necrosis. There were six men and four women, ranging in age between 18 and 87 years (mean, 45 years) (Table). Six of the ten patients had been wearing contact lenses. Three patients had atopic keratoconjunctivitis, but no other predisposing conjunctival disorder was identified. One patient with atopic keratoconjunctivitis wore contact lenses and developed conjunctival necrosis during treatment for suppurative keratitis on two separate occasions.

Nine of the ten patients had received fortified gentamicin sulfate 1.5%. This preparation was in aqueous solution with 0.005% thimerosal in seven patients and unpreserved in two patients. Patients treated with gentamicin sulfate received a second separate antibiotic preparation (Table). Therefore, nine patients received

Accepted for publication Feb. 26, 1991.

From the Department of Clinical Ophthalmology, Moorfields Eye Hospital, London, England.

Reprint requests to C. R. Davison, F.R.C.S., Moorfields Eye Hospital, City Rd., London EC1V 2PD, England.

TABLE
DATA ON TEN PATIENTS WITH CONJUNCTIVAL NECROSIS

CASE NO., AGE (YRS), SEX	ORGANISM	ANTIBIOTIC 1	THIMEROSAL	ANTIBIOTIC 2	ONSET (DAYS)	RESOLVED (DAYS)	CONTACT LENS
1, 38, M	<i>P. aeruginosa</i>	Gentamicin	Yes	Ticarcillin	7	10	Gas permeable
2, 38, M	<i>Streptococcus</i> sp.	Gentamicin	Yes	Cefuroxime	2	13	None
3, 87, F	<i>P. aeruginosa</i>	Gentamicin	Yes	Cefuroxime	5	10	Extended-wear soft
4, 18, M	None	Gentamicin	Yes	Methicillin	5	8	None
5, 75, F	<i>S. aureus</i>	Gentamicin	Yes	Cefuroxime	3	4	Extended-wear soft
6, 73, F	<i>Moraxella</i> sp.	Gentamicin	Yes	Methicillin	5	3	None
7, 23, M	<i>P. aeruginosa</i>	Gentamicin	Yes	Cefuroxime	3	4	Extended-wear soft
8, 42, M*	<i>S. pneumoniae</i>	Gentamicin	No	Ceftazidime	3	4	Gas permeable
	<i>Moraxella</i> sp.	Gentamicin	Yes	None	3	5	Gas permeable
9, 29, F	<i>P. aeruginosa</i>	Tobramycin	No	None	6	5	Extended-wear soft
10, 27, M	<i>S. aureus</i>	Gentamicin	No	Chloramphenicol	11	7	None

*Case 8 was affected on two separate occasions.

multiple topical agents, but gentamicin sulfate was the only agent common to all cases. One patient taking unpreserved fortified tobramycin alone developed a similar conjunctival epithelial defect.

Although all patients initially received the eyedrops at either half-hourly or hourly intervals, the time to onset of conjunctival toxicity varied between two and 11 days, with a mean of 4.8 days. A minimum treatment of 36 drops before the appearance of conjunctival necrosis was seen in the patient who had also received a subconjunctival injection; the mean dose before the development of necrosis was 109 drops (112 mg equivalent). Stinging upon instillation of eyedrops, with chemosis and a mucous discharge, often signaled the onset of conjunctival

toxicity. The most frequent site of the epithelial defects was the inferior bulbar conjunctiva (Fig. 1), although the superior conjunctiva was involved in one patient (Fig. 2). There was typically a pale area of bulbar conjunctiva between 5 and 10 mm from the corneoscleral limbus, which stained with fluorescein. In some patients there was an overlying adherent mucous plaque.

After the recognition of conjunctival toxicity, the strength and frequency of the aminoglycoside eyedrops were reduced, or they were replaced with an alternative antibiotic selected according to the sensitivity of bacterial isolates. The conjunctival defects then healed completely over a period of five to 13 days (mean, seven days).

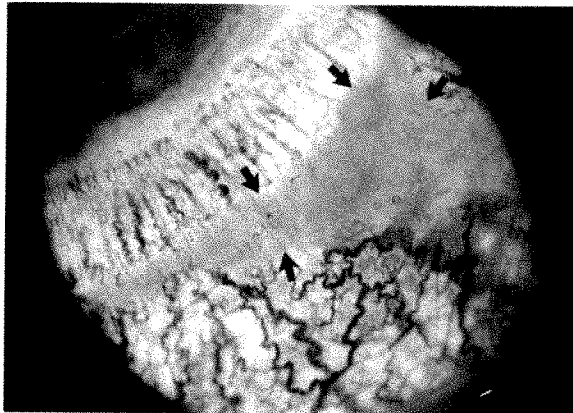
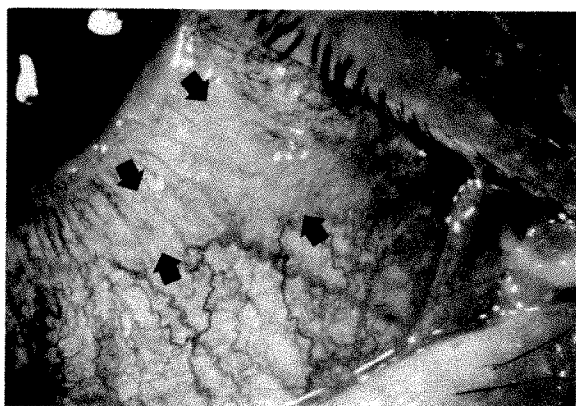


Fig. 1 (Davison, Tuft, and Dart). Case 7. Left, Inferior bulbar conjunctiva of a 23-year-old patient who developed an area of conjunctival epithelial necrosis three days after hourly treatment with 1.5% gentamicin sulfate. Right, The same area highlighted with cobalt blue light after fluorescein instillation demonstrating epithelial cell loss.

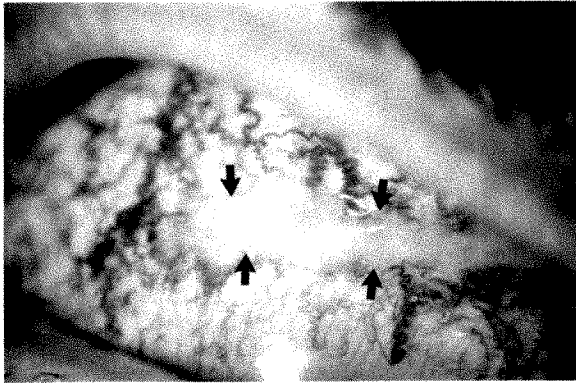


Fig. 2 (Davison, Tuft, and Dart). Case 8. A 42-year-old patient with atopic keratoconjunctivitis who wore a rigid contact lens for correction of keratoconus. Epithelial necrosis developed on the superior bulbar conjunctiva after three days of hourly treatment with nonpreserved gentamicin sulfate 1.5% for a *Pseudomonas* species keratitis.

Discussion

The treatment of suppurative keratitis is usually initiated before culture results are available, and the choice of antibiotics is based on the most likely sensitivity of suspected bacteria.¹⁵ Although higher peak tissue levels can be produced by subconjunctival injection,² the hourly administration of topical fortified aminoglycosides is as effective at eliminating susceptible pathogens.¹⁶⁻²¹ Fortified preparations of gentamicin sulfate or tobramycin are recommended for topical treatment because animal models of suppurative keratitis have shown that standard-strength preparations do not produce bactericidal tissue concentrations when given topically.¹⁶ Fortified eyedrops, however, do carry a substantially greater risk of ocular toxicity when compared with standard-strength preparations.

We think that these lesions represent epithelial necrosis with secondary mucous deposition and masking of underlying vessels. An anterior segment fluorescein angiogram performed in one patient demonstrated patent vessels across the affected areas (unpublished data).

We believe that the location of most lesions in the inferior bulbar conjunctiva reflects the site of maximum drug exposure. The one patient who developed a superior bulbar conjunctival lesion (Fig. 2) had severe atopic keratoconjunctivitis with giant papillae on the superior tarsal conjunctiva. This may have resulted in reduced

tear exchange and increased drug exposure to the affected area.

The mechanism of aminoglycoside toxicity is probably a nonspecific inhibition of protein synthesis in the cells of the conjunctiva. Electron micrographs of conjunctiva after subconjunctival administration of aminoglycosides show overloading of the lysosomes of fibroblasts with phospholipids, and similar changes are seen in the proximal convoluted tubules of patients with gentamicin sulfate-induced acute renal tubular necrosis.^{22,23}

Although we cannot exclude the possibility that other agents or combinations of agents were responsible, the aminoglycosides were probably the cause of the conjunctival necrosis. Thimerosal, used in both of the aminoglycoside preparations, can produce conjunctival and corneal epithelial toxicity. Gasset and associates,²⁴ however, showed that significant toxicity to rabbit corneal epithelium was only seen at concentrations 100 times those used in clinical practice. Of the 11 episodes, three occurred with unpreserved aminoglycoside, and a similar appearance was seen when aminoglycosides were used in combination with five different antibiotics. The aminoglycoside was the only agent to which every patient was exposed.

It is unlikely that the conjunctival defects were caused by the underlying corneal infection for the following reasons: no patients were noted to have any signs of conjunctival necrosis at the initial examination; the site of corneal ulceration bore no relationship to the site of the conjunctival epithelial defects; and diverse organisms were responsible for the corneal infections seen.

The aminoglycosides are more toxic than the recently developed broad-spectrum penicillins and cephalosporins, but they remain the treatment of choice when a gram-negative bacterial corneal infection is suspected. Clinicians should be aware of signs of aminoglycoside toxicity, such as conjunctival necrosis and delayed corneal healing. An aminoglycoside can then be used at a reduced frequency, or a less toxic antibiotic, such as a penicillin or a cephalosporin, can be substituted when the clinical response or bacterial sensitivities allow.

Less toxic broad-spectrum alternatives to the aminoglycosides, such as the quinolones, are becoming available for ophthalmic use and should be evaluated as first-choice antibiotics for suppurative keratitis. The continued use of topical aminoglycosides for conjunctival toxicity is likely to prolong the time to full recovery.

References

1. Wilhelmus, K., Gilbert, M., and Osato, M.: Tobramycin in ophthalmology. *Surv. Ophthalmol.* 32:111, 1987.
2. Glasser, D. B., and Hyndiuk, R. A.: Antibacterial agents. In Tabbara, K. F., and Hyndiuk, R. A. (eds.): *Infections of the Eye*. Boston, Little, Brown & Company, 1986, pp. 211-238.
3. Smolin, G. R., Okumoto, M., and Wilson, F. M., II: The effect of tobramycin on gentamicin-resistant strains in *Pseudomonas keratitis*. *Am. J. Ophthalmol.* 77:583, 1974.
4. Laibson, P., Michaud, R. E., Smolin, G., Okumoto, M., Rosenthal, A., and Cagle, G.: A clinical comparison of tobramycin and gentamicin sulfate in the treatment of ocular infections. *Am. J. Ophthalmol.* 92:836, 1981.
5. Leibowitz, H., Hyndiuk, R., Smolin, G., Nozik, R., Hunter, G., Cagle, G., and Davis, D.: Tobramycin in external ocular disease. A double masked study vs gentamicin. *Curr. Eye Res.* 1:259, 1981.
6. Wilson, L., Weinstein, A., Wood, T., Lindsay, C., and Scott Davis, D.: Treatment of external eye infections. A double blind trial of tobramycin and gentamicin. *J. Ocul. Ther. Surv.* 1:364, 1982.
7. Cagle, G., Davis, S., Rosenthal, A., and Smith, J.: Topical tobramycin and gentamicin sulfate in the treatment of ocular infections. Multicenter study. *Curr. Eye Res.* 1:523, 1982.
8. Hyndiuk, R. A., Skorich, D. N., and Burd, E. M.: Bacterial keratitis. In Tabbara, K. F., and Hyndiuk, R. A. (eds.): *Infections of the Eye*. Boston, Little, Brown & Company, 1986, pp. 303-330.
9. Baum, J.: Therapy for ocular bacterial infection. *Trans. Ophthalmol. Soc. U.K.* 105:69, 1986.
10. Wilson, F.: Adverse external ocular effects of topical ophthalmic medications. *Surv. Ophthalmol.* 24:57, 1979.
11. ———: Adverse external ocular effects of topical ophthalmic therapy. An epidemiologic, laboratory, and clinical study. *Trans. Am. Ophthalmol. Soc.* 81:854, 1983.
12. Stern, G., Schemmer, G., Farber, R., and Gorovoy, M.: Effect of topical antibiotic solutions on corneal epithelial wound healing. *Arch. Ophthalmol.* 101:1775, 1983.
13. Petroutsos, G., Guimaraes, R., Giraud, J., and Pouliquem, Y.: Antibiotics and corneal epithelial wound healing. *Arch. Ophthalmol.* 101:644, 1983.
14. Nauheim, R., Nauheim, J., and Merrick, N.: Conjunctival defects associated with gentamicin. *Arch. Ophthalmol.* 105:1321, 1987.
15. Baum, J., and Jones, D.: Initial therapy of suspected microbial corneal ulcers. *Surv. Ophthalmol.* 24:97, 1979.
16. Gilbert, I., Wilhelmus, K., and Osato, M.: Comparative bioavailability and efficacy of fortified topical tobramycin. *Invest. Ophthalmol. Vis. Sci.* 28:881, 1977.
17. Baum, J., and Barza, M.: Topical vs subconjunctival treatment of bacterial corneal ulcers. *Ophthalmology* 90:162, 1983.
18. Davis, S., Sarff, L., and Hyndiuk, R.: Experimental *Pseudomonas keratitis*. An evaluation of some factors that potentially enhance efficacy. *Arch. Ophthalmol.* 96:123, 1978.
19. Kupferman, A., and Leibowitz, H.: Topical antibiotic therapy of *Pseudomonas aeruginosa keratitis*. *Arch. Ophthalmol.* 97:1699, 1979.
20. Barza, M., Kane, A., and Baum, J. L.: Regional differences in ocular concentration of gentamicin after subconjunctival and retrobulbar injection in the rabbit. *Am. J. Ophthalmol.* 83:407, 1977.
21. Oakley, D. E., Weeks, R. D., and Ellis, P. P.: Corneal distribution of subconjunctival antibiotics. *Am. J. Ophthalmol.* 81:307, 1976.
22. Libert, J., Ketelbant-Balasse, P. E., Van Hoof, F., Aubert-Tulkens, G., and Tulkens, P.: Cellular toxicity of gentamicin. *Am. J. Ophthalmol.* 87:405, 1979.
23. Oshima, M., Hashiguchi, M., Shindo, N., and Shibata, S.: Biochemical mechanisms of aminoglycoside toxicity. *J. Biochem.* 100:1575, 1986.
24. Gasset, A. R., Ishii, Y., Kaufman, H. E., and Miller, T.: Cytotoxicity of ophthalmic preservatives. *Am. J. Ophthalmol.* 78:98, 1974.

Isolated Neurofibromas of the Conjunctiva

Paul H. Kalina, M.D., George B. Bartley, M.D., R. Jean Campbell, M.D.,
and Helmut Buettner, M.D.

We studied four histologically verified cases of isolated neurofibromas of the conjunctiva. The histologic pattern was diffuse in two patients, plexiform in one patient, and solitary in one patient. Simple excision was curative in all cases. We emphasize the importance of distinguishing neuromas (which may be associated with multiple endocrine neoplasia) from neurofibromas.

NEUROFIBROMATOSIS, classified as a phacomatosis, is an autosomal-dominant, inherited disorder with virtually complete penetrance but variable expressivity.¹ Occurring about once in 3,000 births, neurofibromatosis affects approximately 100,000 persons in the United States.^{2,3} The defining clinical features of classic, or type 1, neurofibromatosis, which bears von Recklinghausen's name since his description in 1882,⁴ are café-au-lait spots, freckles of the intertriginous regions of the skin, neurofibromas, and pigmented iris hamartomas or Lisch nodules.⁵ Associated characteristic features may be macrocephaly, pseudarthrosis, bone thinning or dysplasia, short stature, occurrence of various malignant tumors, pheochromocytoma, visceral tumors, intellectual handicaps, cerebrovascular disorders, and central nervous system tumors.¹ Neoplasms involving the central nervous system include optic gliomas and other astrocytomas, neurofibromas, meningiomas, neurilemmomas, and acoustic neuromas. When acoustic neuromas occur bilaterally and are associated with café-au-lait spots, the separate and distinct entity of central, or acoustic, neurofibromatosis (type 2) should be considered.

Neurofibromas, which are composed of proliferations of peripheral nerve elements, predominantly Schwann cells, are the hallmark of neurofibromatosis. They may occur on the body surface as solitary or multiple lesions and appear either as dome-shaped or pedunculated dermal lesions or as subcutaneous nodules along the course of nerves. Neurofibromas are also found in ocular and periocular tissues. They may involve the eyebrow, eyelids, conjunctiva, iris, choroid, optic nerve, and orbit.⁴⁻¹⁰ Neurofibromas of the bulbar and tarsal conjunctiva were recognized as early as the turn of the century.^{7,8} Judging from these and subsequent single case reports,⁹⁻¹⁵ however, they are a rare occurrence in neurofibromatosis. We studied four cases of histologically verified conjunctival neurofibromas.

Patients and Methods

Two patients (Cases 1 and 2) were treated by one of us (G.B.B.); a review of the medical records of our institution identified two additional patients with biopsy-proven isolated neurofibromas of the conjunctiva (Table 1). Patients with conjunctival extension of primary orbital neurofibromatosis were excluded.

Case 1

In 1977, a 14-year-old boy had the central form of neurofibromatosis (type 2). In addition to bilateral acoustic neuromas, he had extramedullary meningiomas, cervical cord neurofibromas, and multiple skin neurofibromas. A 3 × 4-mm, slightly raised, epibulbar lesion was noted at the 5 o'clock meridian at the corneoscleral limbus of the left eye. The clinical diagnosis was neurofibroma. Treatment was not thought to be necessary, and observation was recommended.

During the next 11 years, the mass gradually increased in size, and dry eye symptoms developed. By 1988 the lesion measured 8 × 10 mm and clinically resembled an epibulbar der-

Accepted for publication Feb. 26, 1991.

From the Department of Ophthalmology, Mayo Clinic and Mayo Foundation, Rochester, Minnesota. This study was supported in part by an unrestricted grant from Research to Prevent Blindness, Inc.

Reprint requests to George B. Bartley, M.D., Department of Ophthalmology, Mayo Clinic, 200 First St. S.W., Rochester, MN 55905.

TABLE 1
CLINICAL AND PATHOLOGIC FEATURES OF PATIENTS WITH ISOLATED NEUROFIBROMA OF THE CONJUNCTIVA

CASE NO., AGE (YRS), SEX	SYMPTOMS	APPEARANCE	LOCATION	VISUAL ACUITY	NEUROFIBROMA (TYPE)	HISTOPATHOLOGIC CHARACTERISTICS
1, 14, M	Foreign body sensation dry eye, and growth of lesion	Solid, nodular, tan	Inferotemporal corneoscleral limbus, L.E.	20/20	Yes (2)	Plexiform neurofibroma
2, 35, F	Foreign body sensation	Solid, nodular, pink	Upper tarsal conjunctiva, R.E.	1/200 (optic nerve meningocele)	Yes (1)	Diffuse neurofibroma
3, 34, M	None	Solid, nodular, tan	Temporal corneoscleral limbus, L.E.	20/20	No	Solitary neurofibroma
4, 44, F	None	Solid, gray-white, diagnosed as pterygium	Corneoscleral limbus, L.E.	Counting fingers at 6 ft (amblyopia)	Yes (1)	Diffuse neurofibroma

moid (Fig. 1). The corneal epithelial surface was irregular adjacent to the mass. The patient requested its excision.

During the operation the mass was found to be located in the epibulbar plane without firm attachments to the sclera. Microscopy showed an unencapsulated mass that consisted of an admixture of proliferating endoneural fibroblasts, Schwann cells, and axons arranged in an organoid pattern; individual units were surrounded by a perineurium. Acid mucopolysaccharide material was identified within the endoneurium with Alcian blue stain (Fig. 2). No recurrence has been noted during a two-year follow-up period.

Case 2

A 35-year-old woman with type 1 neurofibromatosis was examined in 1987 for a foreign

body sensation of the right eye. The examination disclosed bilateral Lisch nodules and long-standing decreased vision and optic disk pallor of the right eye secondary to an optic nerve meningocele. A small nodule was identified at the superior tarsal border of the right upper eyelid (Fig. 3) and was thought to be the cause of the foreign body sensation. The lesion was excised, and histopathologic examination showed an unencapsulated neurofibroma of the diffuse type consisting of proliferating nerve elements admixed with collagen. The stroma was minimally myxoid and showed faint staining of mucopolysaccharide with Alcian blue stain (Fig. 4). The ocular discomfort resolved, and no recurrence has been noted during a three-year follow-up period.



Fig. 1 (Kalina and associates). Case 1. Conjunctival neurofibroma at inferotemporal corneoscleral limbus of the left eye. Clinical appearance is suggestive of ocular dermoid.

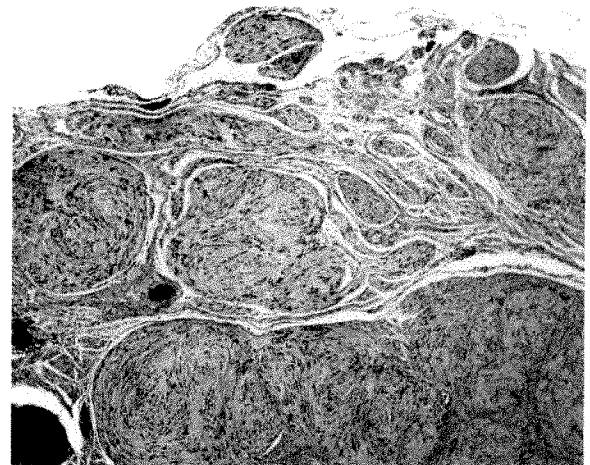


Fig. 2 (Kalina and associates). Case 1. Plexiform neurofibroma showing organoid pattern created by proliferation of peripheral nerve terminal branches (Alcian blue, ×63).



Fig. 3 (Kalina and associates). Case 2. Conjunctival neurofibroma near superior tarsal border of right upper eyelid.

Discussion

Conjunctival neurofibromas are rare (Table 2). In 1898, Katz⁷ reported a case of a plexiform neurofibroma involving the right upper eyelid and orbit in a 12-year-old girl. He described the tarsal conjunctiva as diffusely thickened and swollen but without focal tumefaction or thickening. The earliest histopathologic description of conjunctival neurofibromatosis is attributed to von Michels.⁸ He noted gray-red translucent strands of small nodules arranged parallel to the corneoscleral limbus in the temporal bulbar conjunctiva of a patient with buphthalmos and ipsilateral upper eyelid involvement by neurofibromatosis. Microscopically, these conjunctival changes proved to be small fibromas of a large conjunctival nerve. The superficial conjunctival stroma was infiltrated by small cells, and the epithelium was normal.⁸ Similar observations were made by others.⁹⁻¹¹

Loos¹⁰ described a 36-year-old woman with thickened and blepharoptotic eyelids, papillomatous tumors of the oral mucosa and tip of the tongue, multiple excrescences resembling warts that caused thickening of the upper eyelid margins and conjunctiva, and prominently thickened corneal nerves. In all probability, this case did not represent neurofibromatosis, as claimed by the author, but multiple endocrine neoplasia, type 2B.¹² The mucosal tumors in multiple endocrine neoplasia, which is also characterized by medullary thyroid carcinoma and pheochromocytoma, are neuromas. Froboese¹³ and Wagenmann¹⁴ histologically differentiated neuromas from neurofibromas in a

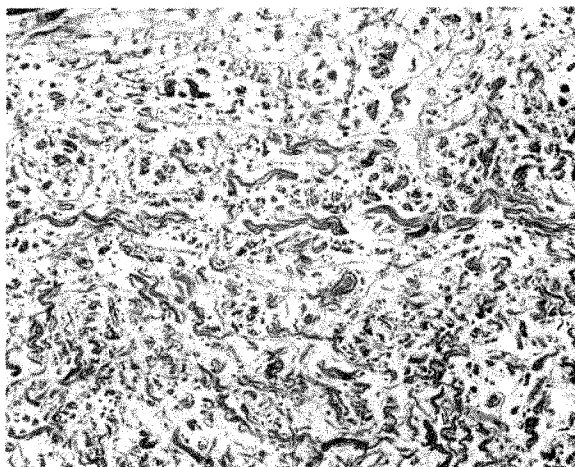


Fig. 4 (Kalina and associates). Case 2. Diffuse type of neurofibroma. An admixture of myelinated axons and collagen in a nonorganoid pattern is seen (Alcian blue, $\times 63$).

classic case of what most likely would now be recognized as multiple endocrine neoplasia.

Conjunctival neurofibromas have been reported by Ibanez Puiggari and Gaviña Alvarado,¹⁵ Soriano and Picoli,¹⁶ Páez-Allende,¹⁷ Dabezies and Penner,¹⁸ Lewis and Riccardi,¹⁹ Perry,²⁰ Insler, Helm, and Napoli,²¹ and Huson, Jones, and Beck.² The cases reported by Ibanez Puiggari and Gaviña Alvarado¹⁵ and by Soriano and Picoli¹⁶ were actually secondary to invasion from upper eyelid neurofibromas and not truly isolated conjunctival neurofibromas. No details were given by Lewis and Riccardi¹⁹ or by Huson, Jones, and Beck² about their cases of conjunctival involvement. A conjunctival schwannoma was reported by Vincent and Cleasby.²²

The predominant clinical finding of these reported cases was an isolated conjunctival nodule, and the most common reason for coming to the clinic was growth. The age at manifestation was younger than 32 years in each case. With the exception of the patient described by Dabezies and Penner,¹⁸ simple excision was uniformly successful.

In our patients, the conjunctival neurofibromas were clinically diagnosed in the second and third decades of life and occurred in two females and two males. The left eye was involved in three of the four patients. The primary reason for ophthalmic consultation was growth of the lesion. Growth was slow and caused no serious clinical problems. Clinically, the neurofibromas were elevated in all patients and were perilimbal in three of the four pa-

TABLE 2
SUMMARY OF PUBLISHED REPORTS OF ISOLATED NEUROFIBROMA OF CONJUNCTIVA*

REFERENCE	AGE (YRS), SEX	APPEARANCE	LOCATION	MANAGEMENT	PATHOLOGIC CHARACTERISTICS	NEUROFIBROMATOSIS
Katz, 1898 ⁷	12, F	Diffusely thickened conjunctiva	Tarsal conjunctiva, upper eyelid, R.E.	Eyelid excision	Eyelid neurofibroma; conjunctiva not described	Yes
von Michels, 1908 ⁸	NA	Gray-red corneoscleral limbus, parallel strands of conjunctiva	Temporal bulbar conjunctiva	Biopsy	Neurofibroma of conjunctival nerve	Yes
Guist, 1920 ⁹	45, M	Gray-red nodules	Tarsal conjunctiva, both eyes, temporal bulbar conjunctiva	Biopsy	Neurofibroma of conjunctival stroma	Yes
Loos, 1932 ¹⁰	36, F	Yellow strands	Temporal perilimbal bulbar conjunctiva, both eyes	Excision	Plexiform neurofibroma (probable neuromas)	No (probable multiple endocrine neoplasia)
Winkelman, 1947 ¹¹	3, M	Opaque, diffusely thickened conjunctiva	Perilimbal bulbar conjunctiva, L.E.	Biopsy	Neurofibroma	Yes
Soriano and Picoli, 1935 ¹⁶	No detailed description of the case					
Páez-Allende, 1945 ¹⁷	18, F	Round, smooth-surfaced, pale pink and salmon-colored lesions	Superior and nasal conjunctiva and cornea, R.E.	Biopsy	Neurofibroma	Yes
Dabezies and Penner, 1961 ¹⁸	50, F	Firm, gray, nodular mass	Superior temporal bulbar conjunctiva, L.E.	Excision x3	Neurofibroma	No
Lewis and Riccardi, 1981 ¹⁹	No detailed description of the five eyes					
Perry, 1982 ²⁰	22, F	Lobulated, yellow-white tumor	Episcleral, subconjunctival, R.E.	Excision	Neurofibroma	No
Insler, Helm, and Napoli 1985 ²¹	24, M	Salmon-pink tumors	Superior perilimbal conjunctiva, both eyes	Biopsy	Hamartoma	Yes
Huson, Jones, and Beck, 1987 ²	No detailed description of the single case					

*NA indicates not available.

tients. Only one of the four patients (Case 3) did not have other signs of generalized neurofibromatosis. Treatment in each instance involved simple excision with histopathologic confirmation of the diagnosis. No recurrence was reported in any of our four cases.

Both the clinical and the pathologic diagnosis may be difficult. A bulbar conjunctival neurofibroma could be clinically suspected to be a dermoid cyst (Fig. 1). In some cases, lymphoma may be considered in the differential diagnosis.²⁰ The preoperative diagnosis of conjunctival

lymphangioma was made by Winkelman¹¹ in another case of conjunctival neurofibromatosis. The lesion in one patient (Case 4) was thought to be consistent clinically with a pterygium.

Histopathologic distinction is among plexiform, diffuse, and solitary types of neurofibroma. The plexiform variant consists of a proliferation of the terminal branches of the peripheral nerve that are arranged in an organoid pattern (Fig. 2); this type is pathognomonic of von Recklinghausen's disease. The diffuse type (Fig. 4), which consists of an admixture of

myelinated axons and collagen but in a non-organoid pattern, is less likely to be associated with von Recklinghausen's disease. In all variants of neurofibroma, the perineural cells predominate over the Schwann cells and axons, and some degree of mucopolysaccharide within their matrix is present. These features contrast with schwannomas, which lack axons and also are encapsulated. The S100 protein stain may help in making the distinction from other non-neural spindle-cell tumors, such as spindle-cell lipoma and fibrolipoma.

Although rare, neurofibroma of the conjunctiva should be considered in the differential diagnosis of a conjunctival nodule, especially in a patient with systemic neurofibromatosis. Excision is usually not necessary unless a tissue diagnosis is needed in a lesion clinically suggestive of a neoplasm, the patient is troubled by the cosmetic appearance, or the lesion causes significant discomfort or abnormalities in adjacent tissues, especially the cornea.

References

1. Riccardi, V. M.: Von Recklinghausen neurofibromatosis. *N. Engl. J. Med.* 305:1617, 1981.
2. Huson, S., Jones, D., and Beck, L.: Ophthalmic manifestations of neurofibromatosis. *Br. J. Ophthalmol.* 71:235, 1987.
3. Mulvihill, J. J., Parry, D. M., Sherman, J. L., Pikus, A., Kaiser-Kupfer, M. I., and Eldridge, R.: Neurofibromatosis 1 (Recklinghausen disease) and neurofibromatosis 2 (bilateral acoustic neurofibromatosis). *Ann. Intern. Med.* 113:39, 1990.
4. von Recklinghausen, F.: Ueber die multiplen Fibrome der Haut und ihre Beziehung zu den multiplen Neuromen. Berlin, August Hirschwald, 1882, pp. 1-138.
5. Lisch, K.: Ueber Beteiligung der Augen, insbesondere das Vorkommen von Irisknötchen bei der Neurofibromatose (Recklinghausen). *Z. Augenheilkd.* 93:137, 1937.
6. Billroth, T.: Ueber die Entstehung der Fibroide. *Arch. Klin. Chir.* 4:545, 1863.
7. Katz, K.: Ueber ein Rankenneurom der Orbita und des oberen Lides. *Arch. Ophthalmol.* [Liepz.] 45:153, 1898.
8. von Michels, J.: Ueber Veränderungen des Auges und seiner Adnexa bei angeborenem Neurofibrome der Gesichtshaut. *Ber. Dtsch. Ophthalmol. Ges.* 35:6, 1908.
9. Guist, G.: Ein Fall von Recklinghausenscher Erkrankung mit Beteiligung der Lid- und Bulbusbindehaut. *Klin. Monatsbl. Augenheilkd. Stuttg.* 45:850, 1920.
10. Loos, F.: Ueber doppelte Neurofibromatosis der Lider, Konjunktiva und Kornea, der Lippen und der Zunge. *Klin. Monatsbl. Augenheilkd.* 89:184, 1932.
11. Winkelman, J. E.: Neurofibromatosis conjunctivae. *Ned. Tijdschr. Geneesk.* 91:3300, 1947.
12. Robertson, D. M., Sizemore, G. W., and Gordon, H.: Thickened corneal nerves as a manifestation of multiple endocrine neoplasia. *Trans. Am. Acad. Ophthalmol. Otolaryngol.* 79:772, 1975.
13. Froboese, C.: Das aus markhaltigen Nervenfasern bestehende, ganglien-zellenlose, echte Neurom in Rankenform. Zugleich ein Beitrag zu den nervösen Geschwülsten der Zunge und des Augenlides. *Virchows Arch. Pathol. Anat. Physiol.* 240:312, 1922-1923.
14. Wagenmann, A.: Multiple Neurome des Auges und der Zunge. *Ber. Dtsch. Ophthalmol. Ges.* 43:282, 1922.
15. Ibanez Puiggari, M., and Gaviña Alvarado, E. R.: Una observación interesante de enfermedad de Recklinghausen, recidiva post-operatoria. *Semana. Med.* 1:1230, 1933.
16. Soriano, F. J., and Picoli, H.: Dos casos de enfermedad de Recklinghausen. *Arch. Oftalmol. Buenos Aires* 10:620, 1935.
17. Páez-Allende, F.: Diffuse neurofibromatosis (von Recklinghausen's disease) involving the bulbar conjunctiva. Report of a case, with lesions of the skeletal system and skin, bodily asymmetry and intracranial involvement. *Arch. Ophthalmol.* 33:110, 1945.
18. Dabiezies, O. H., Jr., and Penner, R.: Neurofibroma or neurilemmoma of the bulbar conjunctiva. *Arch. Ophthalmol.* 66:73, 1961.
19. Lewis, R. A., and Riccardi, V. M.: von Recklinghausen neurofibromatosis. Incidence of iris hamartoma. *Ophthalmology* 88:348, 1981.
20. Perry, H.: Isolated episcleral neurofibroma. *Ophthalmology* 89:1095, 1982.
21. Insler, M. S., Helm, C., and Napoli, S.: Conjunctival hamartoma in neurofibromatosis. *Am. J. Ophthalmol.* 99:731, 1985.
22. Vincent, N. J., and Cleasby, G. W.: Schwannoma of the bulbar conjunctiva. *Arch. Ophthalmol.* 80:641, 1968.

The Carney Complex With Ocular Signs Suggestive of Cardiac Myxoma

Robert H. Kennedy, M.D., Joseph C. Flanagan, M.D., Ralph C. Eagle, Jr., M.D.,
and J. Aidan Carney, M.D.

We treated a patient who had ocphthalmic findings of the Carney complex that led to a search for and the discovery of asymptomatic cardiac myxoma. Substantial morbidity and mortality are associated with the complex because of the occurrence of cardiac myxoma. Facial and eyelid lentiginos, conjunctival and caruncle pigmentation and eyelid pigmentation may precede signs or symptoms of cardiac myxoma. A study of the patient's primary relatives disclosed manifestations of the complex transmitted in a manner consistent with mendelian autosomal dominant inheritance.

KENNEDY, WALLER, AND CARNEY¹ described the ocphthalmic findings in a recently recognized syndrome comprising myxomas, spotty pigmentation, and endocrine overactivity (the Carney complex). Of 63 patients, facial and eyelid lentiginos were observed in 44 (70%), pigmented lesions on the caruncle or conjunctival semilunar fold in 17 (27%), and eyelid myxoma in ten (16%). Early recognition and correct interpretation of these findings is particularly important because the syndrome includes cardiac myxoma and is familial, transmitted as a mendelian dominant trait.¹⁻⁶ Psammomatous mela-

notic schwannoma has been added to the complex.⁷

Nearly half of the patients with the complex of myxomas, spotty pigmentation, endocrine overactivity, and schwannomas developed significant impairment from embolic events or died as a direct result of cardiac myxoma.^{1,2} It is likely that many patients would have survived if the clinically apparent components of the complex had been recognized and interpreted correctly and if appropriate medical examinations had been performed. Correct interpretation of findings has led to examination of the heart of a 58-year-old woman with the characteristic facial, ocphthalmic, and labial pigmentation, and an asymptomatic cardiac myxoma was discovered and removed successfully.³

We treated a patient who was initially examined by two of us (R.H.K., J.C.F.) in the Oculoplastic Department at Wills Eye Hospital. The special ocphthalmic findings prompted more detailed examination of the patient, inquiry concerning his family, and ultimately the recommendation that all undergo further study for the complex. Asymptomatic cardiac myxoma was discovered in our patient, and the complex was diagnosed in several other family members, transmitted in a manner consistent with autosomal dominant inheritance. Improved recognition of the complex by ophthalmologists will facilitate early diagnosis of this condition in other patients, thereby averting much of the associated morbidity and mortality, primarily caused by cardiac myxoma.

Case Report

A 23-year-old man was referred to the Oculoplastic Department at Wills Eye Hospital for examination of swelling and blepharoptosis of the right upper eyelid that had increased gradually for approximately four months. Two or three months before the symptoms began, a

Accepted for publication March 1, 1991.

From the Department of Ophthalmology, University of Texas-Southwestern Medical Center, Dallas, Texas (Dr. Kennedy); Departments of Oculoplastic Surgery (Dr. Flanagan) and Pathology (Dr. Eagle), Wills Eye Hospital, Philadelphia, Pennsylvania; and Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, Minnesota (Dr. Carney). This study was supported in part by a grant from Research to Prevent Blindness, Inc. Dr. Kennedy was a 1988-1989 Heed Ophthalmic Fellow.

Reprint requests to Robert H. Kennedy, M.D., Department of Ophthalmology, University of Texas-Southwestern Medical Center, 5323 Harry Hines Blvd., Dallas, TX 75235-9057.

soft contact lens had been noted to be missing from his right eye, and it was never found. On several occasions during the past few years, single, small lesions had been shaved from the left upper eyelid margin; however, no histologic examination was obtained. Other than myopia, he reported no previous ocular disorders, and his general health was excellent. At the age of 9 years, benign tumors had been excised from both testicles, and there had been no recurrence. Additionally, a few small, nodular skin lesions had been removed from his face and trunk during the past several years.

Ophthalmic examination disclosed a soft, nontender anterior orbital mass superonasally on the right side, which was visible beneath the conjunctiva in the superior fornix and measured 1×2 cm (Fig. 1). Blepharoptosis (4 mm) of the right upper eyelid was present. A small mass (1×2 mm) was observed on the margin of the left upper eyelid centrally (Fig. 2). Results of the remainder of the ophthalmic examination were normal, and best-corrected visual acuity was 20/20 in both eyes.

The right orbital mass was removed through a conjunctival incision placed superior to the tarsus. The yellow mass had a gelatinous texture and was not encapsulated. Histologic examination showed loose, myxoid areas that alternated with areas of spindle cells and collagen fragments (Fig. 3). After careful review, the diagnosis of myxoma was established. Postoperatively, the patient recovered well, and the blepharoptosis resolved.

The presence of an orbital myxoma suggested that the patient might have the complex of

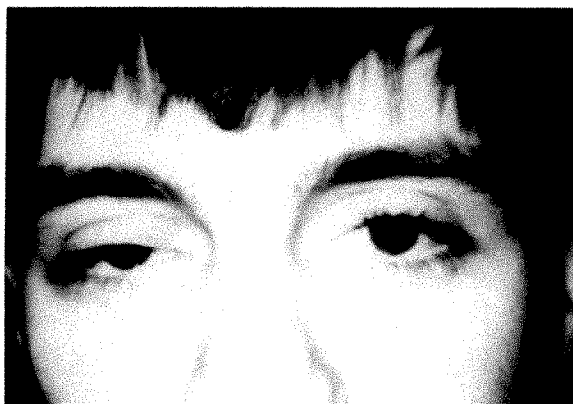


Fig. 1 (Kennedy and associates). Anterior orbital mass superonasally with associated blepharoptosis of right upper eyelid that microscopically proved to be a myxoma.



Fig. 2 (Kennedy and associates). Small mass on margin of left upper eyelid that microscopically proved to be a myxoma.

myxomas, spotty pigmentation, endocrine overactivity, and schwannomas. Therefore, the patient's skin was examined for pigmented spots; a few lentigines were present on the trunk, but none were on his face. The small mass on the left upper eyelid was removed several weeks later, and it also proved to be a myxoma.

The family history disclosed that two of the patient's four brothers had also had benign tumors removed from their testicles. Additionally, the patient's father (who had died several years previously of probable carcinoma of the pancreas) had many nodular and pigmented skin lesions on his face and trunk. His mother, sister, and two additional brothers were in good health and had no outwardly visible signs suggestive of the diagnosis of the complex. Review of pathologic records and histologic slides of family members disclosed that the father had multiple cutaneous myxomas and cutaneous lentigines. Two brothers, as well as the patient, had large-cell calcifying Sertoli cell tumors of the testis; one brother also had cutaneous lentigines, and the other had multiple cutaneous myxomas and psammomatous melanotic schwannoma of the thigh.⁷

The patient was referred for cardiac examination. Echocardiography disclosed a mass in the left ventricle. During the operation, a second smaller mass in the left ventricle was also found and removed. Histologic examination showed that both tumors were cardiac myxomas. The patient recovered well from the operation, and he has had no cardiac difficulties during the 16 postoperative months. The right orbital myxoma, however, recurred and was removed 12

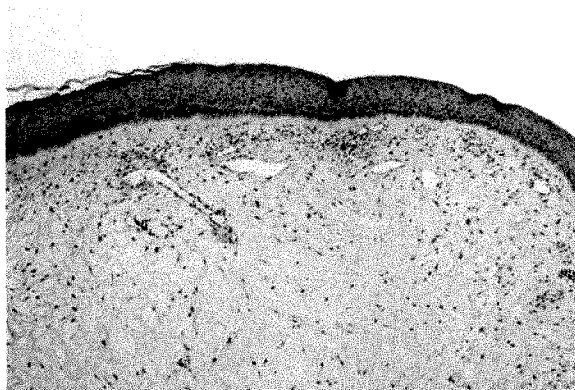


Fig. 3 (Kennedy and associates). Eyelid myxoma. Hypocellular myxomatous mass composed of ground substance, collagen fibers, and some dilated capillaries (hematoxylin and eosin, $\times 100$).

months after the initial operation. His siblings and mother had normal results of medical examinations (except for findings documented from review of previous surgical specimens) and results of echocardiography.

We advised the patient and his family of the mendelian dominant mode of inheritance and discussed the implications for any children they might eventually have (Fig. 4). Because the cardiac myxomas that occur in association with the complex tend to be multiple and recurrent, we advised them of the need for continued follow-up to detect additional myxomas.

Discussion

Carney⁸ showed that there are two established types of cardiac myxomas, nonfamilial (sporadic) and familial. In his study, 48 of 51 patients (94%) treated at the Mayo Clinic had the nonfamilial type. It commonly occurred during the fifth and sixth decades (average age, 52 years); 36 (75%) were women; 42 (87%) had a single tumor in the left atrium; and none had other unusual conditions. Conversely, familial cardiac myxoma usually occurred in the second and third decades (average age, 24 years) in 24 previously described patients.⁸ Of these 24 patients, 15 (62%) had tumor in the left atrium, eight (33%) had multicentric tumors, and five (21%) had unusual associated conditions. The associated conditions included other myxomas (cutaneous and mammary), spotty skin pigmentation (lentigines and blue nevi), endocrine overactivity (Cushing's syndrome, sexual pre-

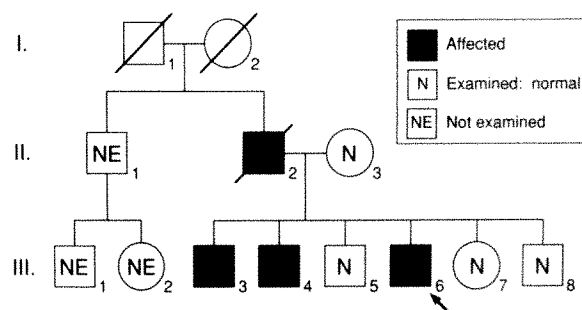


Fig. 4 (Kennedy and associates). Pedigree of family. Arrow identifies proband; squares indicate males; circles indicate females; diagonal line through symbol indicates deceased. The paternal grandparents, uncle, and first cousins were not known to have any manifestation of the complex.

cocity, and acromegaly), and schwannomas. Together these conditions constitute a syndrome transmitted as a dominant trait that has been called the Carney complex.⁹ Cutaneous myxoma has occurred in 22 of 41 patients (54%) with the complex, was multicentric in 16 (73%), and had a predilection for the eyelids, ears, and nipples.¹⁰

The ophthalmic findings associated with the complex include spotty pigmentation of the eyelids and face, pigmented lesions of the caruncles, and eyelid myxomas.^{1,2} Most patients with the complex develop one or more of those findings during the first decade of life. Among patients who have had cardiac myxoma, the ophthalmic manifestations have generally preceded the onset of any signs or symptoms of cardiac myxoma by several years. Consequently, early recognition by ophthalmologists of the significance of the ophthalmic findings and referral for medical examination could help to prevent much of the morbidity and mortality related to cardiac myxoma.

Several factors, however, make early identification of patients with the complex difficult. The complex is a relatively uncommon disorder, but spotty pigmentation of the eyelids and face caused by ephelides is common. Although the pigmented lesions associated with the complex are lentigines, clinical differentiation between ephelides and lentigines can be difficult. Therefore, referral of all patients with spotty pigmentation for cardiac examination would likely not prove to be an efficient screening strategy, and we would not recommend it. Factors that should increase suspicion include the presence of dark or black lesions, not induced by sun exposure, on the caruncle, conjunctival

semilunar fold, or vermilion border of the lips in young patients. Suspicion should be heightened further if any other features suggestive of the complex are also present. In our view, any patient who has had myxoma of the eyelid should be referred for medical examination including echocardiography regardless of whether any other outwardly visible components of the complex are present. Most of the eyelid myxomas that have been reported have occurred in patients with the complex.^{1,11-13} We reported previously that of ten patients with eyelid myxoma occurring in association with the complex, seven developed cardiac myxoma.¹ Also, all first-degree relatives of patients with the complex should be advised of the need for continued medical examination.

Of the 63 patients previously described,¹ 44 (70%) had spotty pigmentation of the skin; 44 (70%) had cardiac myxomas; 29 (46%) had skin myxomas; 13 (21%) had breast myxomas; 22 (35%) had Cushing's syndrome; six (10%) had pituitary growth hormone-secreting adenoma; and 12 of 27 males (44%) had testicular tumors. Not all patients develop all of the features, but two or more of the following conditions occurring in characteristic fashion are required to establish diagnosis of the syndrome: myxomas (cardiac, cutaneous, or mammary); spotty skin pigmentation (lentigines and blue nevi); Cushing's syndrome (caused by primary pigmented nodular adrenocortical disease); acromegaly or gigantism (the result of growth hormone-producing pituitary adenoma); sexual precocity (caused by large-cell calcifying Sertoli cell tumor of the testis, Leydig cell tumor of the testis, or adrenocortical rest tumor); or psammomatous melanotic schwannoma.^{1,2,5,7,10}

The mode of inheritance of the complex of myxomas, spotty pigmentation, endocrine overactivity, and schwannomas has been reported to be mendelian dominant.³ The finding of transmission of the complex from father to son was not observed in that study, however, and is required to confirm that the mode of inheritance is autosomal dominant. Bain⁴ mentioned that he had identified a family with an affected father and son. The findings in our patient and in his brothers and father support

the concept that the mode of inheritance of the syndrome is autosomal dominant.

References

1. Kennedy, R. H., Waller, R. R., and Carney, J. A.: Ocular pigmented spots and eyelid myxomas. *Am. J. Ophthalmol.* 104:533, 1987.
2. Carney, J. A., Gordon, H., Carpenter, P. C., Shenoy, B. V., and Go, V. L. W.: The complex of myxomas, spotty pigmentation, and endocrine overactivity. *Medicine* 64:270, 1985.
3. Carney, J. A., Hruska, L. S., Beauchamp, G. D., and Gordon, H.: Dominant inheritance of the complex of myxomas, spotty pigmentation, and endocrine overactivity. *Mayo Clin. Proc.* 61:165, 1986.
4. Bain, J.: Carney's complex (letter to the editor). *Mayo Clin. Proc.* 61:508, 1986.
5. McCarthy, P. M., Piehler, J. M., Schaff, H. V., Pluth, J. R., Orszulak, T. A., Vidaillet, H. J., and Carney, J. A.: The significance of multiple, recurrent, and "complex" cardiac myxomas. *J. Thorac. Cardiovasc. Surg.* 91:389, 1986.
6. Danoff, A., Jormark, S., Lorber, D., and Fleischer, N.: Adrenocortical micronodular dysplasia, cardiac myxomas, lentigines, and spindle cell tumors. Report of a kindred. *Arch. Intern. Med.* 147:443, 1987.
7. Carney, J. A.: Psammomatous melanotic schwannoma. A distinctive, heritable tumor with special associations, including cardiac myxoma and the Cushing syndrome. *Am. J. Surg. Pathol.* 14:206, 1990.
8. ———: Differences between nonfamilial and familial cardiac myxoma. *Am. J. Surg. Pathol.* 9:53, 1985.
9. Young, W. F., Jr., Carney, J. A., Musa, B. U., Wulfraat, N. M., Lens, J. W., and Drexhage, H. A.: Familial syndrome due to primary pigmented nodular adrenocortical disease. Reinvestigation 50 years later. *N. Engl. J. Med.* 321:1659, 1989.
10. Carney, J. A., Headington, J. T., and Su, W. P. D.: Cutaneous myxomas. A major component of the complex of myxomas, spotty pigmentation, and endocrine overactivity. *Arch. Dermatol.* 122:790, 1986.
11. Town, A. E.: Myxoma of the lower eyelid. *Am. J. Ophthalmol.* 28:68, 1945.
12. Bölcs, S., and Juhos, P.: A case of palpebral myxoma. *Ophthalmologica* 171:488, 1975.
13. Daicker, B. C.: Multiple myxome der lider. *Ophthalmologica* 179:125, 1979.

Urine Drug Screening for Cocaine After Lacrimal Surgery

Oscar A. Cruz, M.D., James R. Patrinely, M.D., George S. Reyna, M.D.,
and J. W. King, M.T.

We investigated whether the results of routine urine drug screening for cocaine would be positive after dacryocystorhinostomy. Postoperative urine specimens were analyzed for the presence of benzoylecgonine, the major metabolite of cocaine, by gas chromatography-mass spectrometry. The results of urine tests of all 12 patients were positive for cocaine 24 hours postoperatively. Nine (75%) were positive 48 hours postoperatively, and three (33%) had detectable levels 72 hours after surgery. Patients given cocaine at the time of lacrimal surgery should be warned that they may test positive for cocaine for at least three days postoperatively.

THE CURRENT MEDICAL USES of cocaine are limited to its topical anesthetic and sympathomimetic properties. Rhinologists commonly use it to anesthetize and vasoconstrict nasal and laryngeal mucous membranes.¹ In ophthalmic surgery, cocaine is frequently used in lacrimal drainage surgery for similar purposes.

Although the medical uses of cocaine are well known to the scientific community, it is more widely considered by the public to be a recreational drug that is misused. Urine drug screening has become routine in law enforcement and in the workplace. In routine urine screening, a positive result is considered evidence of illegal cocaine use.

We investigated the results of urine drug screening for cocaine after routine lacrimal surgery. We analyzed urine specimens after lacri-

mal surgery for the presence of benzoylecgonine, the major metabolite of cocaine, in patients undergoing dacryocystorhinostomy.

Patients and Methods

All patients undergoing elective dacryocystorhinostomy examined between September 1989 and April 1990 at hospitals affiliated with the Baylor College of Medicine were recruited for the study. Patients with a history of previous cocaine use, pregnant patients, those who could not give voluntary informed consent, and those who could not arrange or comply with follow-up examinations during the study period were excluded from participation. Five patients were excluded from the study for these reasons. Every patient was tested preoperatively for cocaine, and patients with positive results of a urine test were excluded from the study. All patients underwent dacryocystorhinostomy performed by one of us (J.R.P.). Twelve patients comprised the final study group.

Before surgery, the nasal mucosa was initially constricted with a single spray of aerosolized 4% cocaine. This improved visualization so that the nasal cavity could be packed with 12 to 18 inches of ¼-inch gauze cotton strips lightly soaked in 2 ml of 4% cocaine solution.² Only 1 ml of 4% cocaine was used in infants and children. The gauze was firmly squeezed semi-dry before packing. The packing was placed in the nasal vestibule near the head of the middle turbinate at the planned rhinostomy site.^{3,4} Then the lacrimal surgery was performed as customary. Cardiac, respiratory, and blood pressure levels were monitored throughout the operative and immediate postoperative period. All patients were examined 24 hours postoperatively, and a urine sample was obtained at that time. All patients were then instructed to obtain urine samples 48 hours, 72 hours, and one week postoperatively. The urine samples were analyzed for cocaine metabolites by gas chromatography-mass spectrometry.

Accepted for publication March 6, 1991.

From the Department of Ophthalmology, Cullen Eye Institute (Drs. Cruz, Patrinely, and Reyna), and Division of Plastic Surgery (Dr. Patrinely), Baylor College of Medicine, Houston, Texas; and Southwest Laboratory of Toxicology, Houston, Texas (Mr. King). This study was supported in part by an unrestricted grant to the Baylor College of Medicine from Research to Prevent Blindness, Inc.

Reprint requests to James R. Patrinely, M.D., Cullen Eye Institute, 6501 Fannin, NC200, Houston, TX 77030.

Results

Of the 12 patients who underwent dacryocystorhinostomy, all tested positive postoperatively for cocaine (Table). The levels detected ranged from 67 ng/ml (minimal detection limit, 60 ng/ml) to 2,459 ng/ml. The variability of the amount detected in the urine demonstrated the pronounced dose dependence that is characteristic of cocaine metabolism. Nine of 12 patients (75%) had detectable levels greater than 300 ng/ml at 24 hours (immunoassay detection limit). There was an average decline in benzoylecgonine levels of approximately 80% between the 24-hour and 48-hour samples. Nine of 12 patients (75%) still tested positive at 48 hours. Two of 12 patients (17%) had levels greater than 300 ng/ml; one of these had the only bilateral procedure that was included. Four of 12 patients (33%) had detectable levels of benzoylecgonine at 72 hours after the operation. The results of all one-week urine samples were negative.

Discussion

The current medical use of cocaine is limited to localization of Horner's syndrome and local

TABLE
POSTOPERATIVE BENZOYLECGONINE URINE LEVELS
(NG/ML) AFTER DACRYOCYSTORHINOSTOMY

CASE NO., AGE (YRS), SEX	HOURS POSTOPERATIVELY*		
	24	48	72
1, 35, M	661	108	60
2, 42, F†	568	319	NM
3, 35, M	259	NM	NM
4, 68, M	375	70	NM
5, 62, M	133	93	NM
6, 37, M	2,459	387	88
7, 38, M	121	NA	NM
8, 54, M	662	94	NM
9, 81, M	852	177	72
10, 29, F	67	NM	NM
11, 88, F	1,226	218	68
12, 2, F	1,347	220	NM

*Results of all one-week samples were negative. NM indicates not measurable with a minimum detection limit of 60 ng/ml, and NA indicates not available.

†Case 2 had bilateral surgery.

anesthesia in oculoplastic surgery, bronchoscopy, myringotomy, and rhinoplastic procedures. Bralliar, Skarf, and Owens⁵ demonstrated that the application of two drops of a 10% solution of cocaine hydrochloride, instilled in the conjunctival cul-de-sac, resulted in positive results of urine tests for cocaine with the use of an immunoassay at four, 24, and 36 hours.

Our study demonstrated that a sensitive urine assay combined with the efficient absorption of cocaine across a mucous membrane will result in positive results of urine tests. The levels detected were much higher in terms of possible pharmacologic effects than we anticipated. In routine screening, a positive test result is considered evidence of illegal cocaine use. Although techniques can vary the dosage, 80 to 200 mg of cocaine is generally administered intranasally during packing for dacryocystorhinostomy. The psychoactive dose of cocaine for adults, by intranasal administration, is between 50 and 95 mg.⁶ Factors involved in the range and variability of levels included the variable bioavailability of cocaine as well as weight, liver function, renal function, and hydration status of the patient. Cocaine metabolism has been studied and reviewed extensively.⁷⁻⁹ Barnett, Hawks, and Resnick¹⁰ demonstrated the pronounced dose dependence that affects many pharmacokinetic factors. Bioavailability would also be affected by nasal bleeding during packing.

Gas chromatography-mass spectrometry is generally believed to be the most reliable and sensitive test to detect cocaine and its metabolites and is therefore generally used to confirm positive results of immunoassays and to provide quantification.^{6,11}

Since the presence of cocaine can be detected in the urine up to 72 hours after lacrimal surgery, we recommend that physicians should consider requiring informed consent if they plan to use cocaine during surgery. With more lacrimal surgery being performed on an outpatient basis and patients returning to normal activities soon after the operation, this issue becomes important. All patients must be warned that they may test positive for cocaine for at least three days postoperatively. Although there is no standardized procedure for double-checking positive results of urine tests, some corporations and agencies will request medical review for possible previous medical usage of cocaine or similar substances. Additionally, every attempt should be made to use the minimum amount of topical cocaine necessary.

References

1. Verlander, J. M., and Johns, M. E.: The clinical use of cocaine. *Otolaryngol. Clin. North Am.* 14:521, 1981.
2. Patrinely, J. R., and Gigantelli, J. W.: Dacryocystorhinostomy. In Lindberg, J. V. (ed.): *Contemporary Issues in Ophthalmology*, vol. 5. New York, Churchill Livingstone, 1988, p. 151.
3. Kirshner, H.: Local anesthesia in external dacryocystorhinostomy. In Bosniak, S. L. (ed.): *Advances in Ophthalmic Plastic and Reconstructive Surgery*, vol. 3. Elmsford, New York, Pergamon Press, 1984, pp. 267-271.
4. Patrinely, J. R., and Anderson, R. L.: A review of lacrimal drainage surgery. *Ophthalmic Plast. Reconstr. Surg.* 2:97, 1987.
5. Bralliar, B. B., Skarf, B., and Owens, J. B.: Ophthalmic use of cocaine and the urine test for benzoylecgonine. *N. Engl. J. Med.* 320:1757, 1989.
6. Department of Health and Human Services:

Alcohol, Drug Abuse, and Mental Health Administration. Scientific and technical guidelines for federal drug testing programs, standards for certification of laboratories engaged in urine drug testing for federal agencies. *Fed. Register* 52:30638, 1987.

7. Ambre, J.: The urinary excretion of cocaine and metabolites in humans. A kinetic analysis of published data. *J. Anal. Toxicol.* 9:241, 1985.

8. Hawks, R. L., and Chiang, C. N.: Urine testing for drugs of abuse. *Natl. Inst. Drug Abuse Res. Monogr. Ser.* 73. Washington, D.C., U.S. Government Printing Office, 1986, pp. 8-121.

9. Jatlow, P.: Cocaine. Analysis, pharmacokinetics, and metabolic disposition. *Yale J. Biol. Med.* 61:105, 1988.

10. Barnett, G., Hawks, R., and Resnick, R.: Cocaine pharmacokinetics in humans. *J. Ethnopharmacol.* 3:353, 1981.

11. Hoyt, D. W., Finnigan, R. E., Nee, T., Shults, T. F., and Butler, T. J.: Drug testing in the workplace. Are methods legally defensible? *JAMA* 258:504, 1987.

OPHTHALMIC MINIATURE

And her eyes—ah, you should have seen them and broken your hearts. Have you seen that veiled deep glow, that pathetic hurt dignity, that unsubdued and unsubduable spirit that burns and smoulders in the eye of a caged eagle and makes you feel mean and shabby under the burden of its mute reproach? Her eyes were like that. . . . Yes, at all times and in all circumstances they could express as by print every shade of the wide range of her moods. In them were hidden floods of gay sunshine, the softest and peacefulest twilights, and devastating storms and lightnings.

Mark Twain, *Personal Recollections of Joan of Arc*
Hartford, The Stowe-Day Foundation, 1980, p. 343

Palpebral Fissure Responses to Topical Adrenergic Drugs

Paul M. Munden, M.D., Randy H. Kardon, M.D., Chad E. Denison,
and Keith D. Carter, M.D.

We measured the magnitude and time course of the increase in palpebral fissure width in ten normal volunteers in response to direct-acting (2.5% phenylephrine, 1% apraclonidine) and indirect-acting (10% cocaine, 1% hydroxyamphetamine) topical adrenergic drugs given in one eye. The increase in the palpebral fissure width of the treated eye was compared to the width of the untreated, control eye during a period of 60 minutes after each drug was administered. The difference in fissure width (asymmetry) between the treated and untreated eyes increased significantly for all drugs during the three- to 60-minute time period after treatment. There was no significant difference in the maximum eyelid effect among the adrenergic drugs tested. The drugs exerted their maximum effect by 30 minutes in 39 of the 40 trials (97.5%). The direct-acting drugs tended to exert their effect more quickly than the indirect-acting drugs. Our results demonstrate the expected increase in palpebral fissure width in response to topical adrenergic drugs in normal eyes. This information will provide a basis for evaluating Müller's muscle and its sympathetic innervation in patients with blepharoptosis.

AN INCREASE in the width of the palpebral fissure is frequently noted after the application of topical adrenergic drugs. Some surgeons routinely use topical 2.5% or 10% phenylephrine to assess the contractile status of Müller's muscle before certain blepharoptosis proce-

dures.¹ Eyelid retraction has also been noted with the use of topical apraclonidine.² We have seen increases in the palpebral fissure widths of both the blepharoptotic and normal eyes of patients with Horner's syndrome who receive topical cocaine, hydroxyamphetamine, or phenylephrine. The diagnosis and localization of the sympathetic defect in Horner's syndrome is usually based on the pupil responses to these drugs.³⁻⁷ Since these responses are equivocal at times, we were interested in determining whether palpebral fissure responses to topical adrenergic drugs could be used in a similar fashion to diagnose Horner's syndrome and identify the location of the sympathetic lesion. To do this, it was first necessary to characterize the drug response in normal subjects.

We evaluated palpebral fissure responses to topical 10% cocaine, 1% hydroxyamphetamine, 2.5% phenylephrine, and 1% apraclonidine in a group of ten normal volunteers to determine the time course and degree of effect of these adrenergic drugs.

Cocaine and hydroxyamphetamine are indirect adrenergic agonists. Cocaine exerts its effects by inhibiting reuptake of norepinephrine from the sympathetic nerve endings. Hydroxyamphetamine causes release of norepinephrine from the nerve endings of sympathetic neurons. Phenylephrine is a direct-acting alpha-1 adrenergic agonist, whereas apraclonidine is a direct-acting, peripheral alpha-2 adrenergic agonist. Each of these drugs causes a widening of the palpebral fissure by inducing contraction of the sympathetically innervated muscles of the eyelids.

Accepted for publication March 21, 1991.

From the Department of Ophthalmology, University of Iowa Hospitals and Clinics, Iowa City, Iowa. This study was supported in part by an unrestricted grant from Research to Prevent Blindness, Inc. This study was presented in part at the annual meeting of the Association for Research in Vision and Ophthalmology, Sarasota, Florida, May 4, 1991.

Reprint requests to Randy H. Kardon, M.D., Department of Ophthalmology, University of Iowa Hospitals and Clinics, Iowa City, IA 52242.

Subjects and Methods

Ten normal volunteers with no history of ocular disease or trauma and no allergies to the topical medications were recruited. The legal requirements governing informed consent were followed.

Slit-lamp examination was performed in all

subjects. The right or left eye was selected randomly for pharmacologic testing. The same eye was used for each drug tested. At least 24 hours passed before testing the next drug. The topical medications were tested in the following order: 10% cocaine; 1% hydroxyamphetamine; 2.5% phenylephrine; and 1% apraclonidine. No residual drug effect was noted in any of the volunteers. The lack of residual effect was based on an absence of anisocoria before each drug treatment and the absence of any significant differences in baseline fissure asymmetry among the four tested drugs.

We chose to treat only one eye and use the other, untreated eye as the control. This was done so that any change in voluntary eyelid elevation (even while fixating on a distant target) would affect both fissure sizes equally and not influence the measured drug effect, assuming Hering's law of equal innervation. The effect of each adrenergic drug was therefore expressed in terms of palpebral fissure asymmetry. Fissure asymmetry was calculated by subtracting the measured fissure width of the untreated, control eye from the treated, fellow eye.

Photographs of each subject were taken with a Loewenfeld-Rosskoth camera.⁸ This camera produced 1:1 life-sized images of both eyes with self-developing color film. An adjustable chin rest maintained the distance and height of the eyes constant in relation to the camera lens while the subject looked at a distant fixation light. This method of photography maintained

a fixed alignment of the eye with relation to the camera lens, which eliminated most changes in fissure size caused by voluntary eye movements. The 1:1 life-sized image allowed direct measurement of the fissure width from the photographs by a magnifier with graticule. Baseline photographs were taken of the eyes before drug application. One drop of topical medication was then instilled in the lower fornix of the selected eye. A second drop was instilled ten seconds later. Two photographs of the eyes were taken in succession at intervals of one, three, five, ten, 15, 30, and 60 minutes.

Each photograph was labeled and vertically cut in half between the right and left eyes so that fissure measurements were not biased by the appearance of the fellow eye. The palpebral fissures were measured at their widest point to the nearest tenth of a millimeter by a masked observer using a magnifier with a metric graticule (Edmund Scientific, Paramus, New Jersey).

The average amount of palpebral fissure asymmetry for each time interval was compared to the baseline fissure asymmetry and also to the maximum fissure asymmetry for each drug by repeated measures analysis of variance. The mean baseline fissure asymmetry, mean maximum fissure asymmetry, and mean time to the maximum fissure asymmetry were compared among the different drug treatment groups using the Kruskal-Wallis test for nonparametric data. A P value of less than .05 was considered significant.

TABLE 1
THE MEAN PALPEBRAL FISSURE ASYMMETRY IN TEN SUBJECTS AT EACH TIME INTERVAL*

TIME (MINS)	COCAINE			HYDROXYAMPHETAMINE			PHENYLEPHRINE			APRACLONIDINE		
	MEAN ASYMMETRY (MM)	S.E.	P VALUE	MEAN ASYMMETRY (MM)	S.E.	P VALUE	MEAN ASYMMETRY (MM)	S.E.	P VALUE	MEAN ASYMMETRY (MM)	S.E.	P VALUE
Baseline	0.08	0.1	—	-0.07	0.1	—	0.05	0.1	—	0.06	0.1	—
1	0.01	0.2	.711	-0.01	0.2	.658	0.31	0.2	.06	-0.01	0.1	.44
3	1.03	0.2	.0001	0.41	0.2	.0001	0.95	0.3	.012	0.58	0.1	.0022
5	1.27	0.2	.0001	0.42	0.2	.0016	1.17	0.2	.0018	0.82	0.2	.0005
10	1.34	0.2	.0001	1.10	0.2	.0001	1.46	0.2	.0005	1.20	0.2	.0001
15	1.17	0.2	.0001	0.97	0.2	.0001	1.43	0.3	.001	1.36	0.2	.0001
30	1.48	0.3	.0001	1.31	0.2	.0001	1.01	0.2	.0036	1.27	0.2	.0001
60	1.32	0.2	.0005	0.80	0.2	.0001	0.68	0.2	.031	1.13	0.2	.0006

*The mean asymmetry (treated-control eye) for each time interval is compared to the baseline asymmetry by repeated measures analysis of variance. A negative value means that the mean fissure width was greater for the control eye. S.E. indicates standard error of the mean.

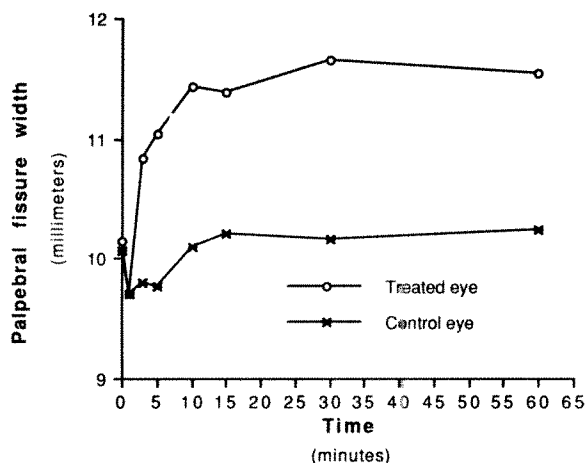


Fig. 1 (Munden and associates). Mean palpebral fissure responses of the control eye and the eye treated with topical 10% cocaine in ten normal subjects.

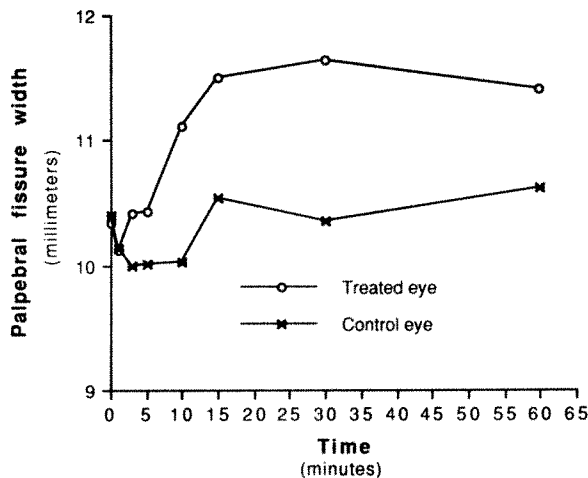


Fig. 2 (Munden and associates). Mean palpebral fissure responses of the control eye and the eye treated with topical 1% hydroxyamphetamine in ten normal subjects.

Results

There were no significant differences in the baseline palpebral fissure widths or in the baseline palpebral fissure asymmetry (treated eye minus untreated eye) among the four drugs tested. The palpebral fissure asymmetry was significantly increased over baseline during the three- to 60-minute time interval for all the drugs tested (Table 1).

The increase in fissure asymmetry occurred more quickly in the phenylephrine group but also began to decline sooner as compared to the cocaine and hydroxyamphetamine groups (Figs. 1 through 5). The average time to maximum effect varied from 23.0 minutes for 1% hydroxyamphetamine to 10.8 minutes for 2.5% phenylephrine (Table 2).

The amount of increase in fissure width was equivalent among the four drugs, since there was no significant difference in the maximum

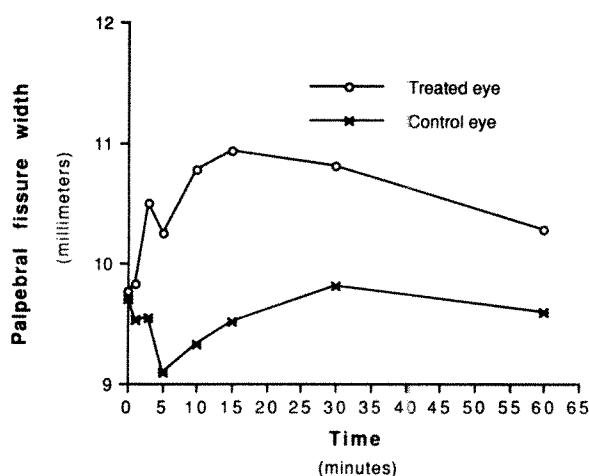


Fig. 3 (Munden and associates). Mean palpebral fissure responses of the control eye and the eye treated with topical 2.5% phenylephrine in ten normal subjects.

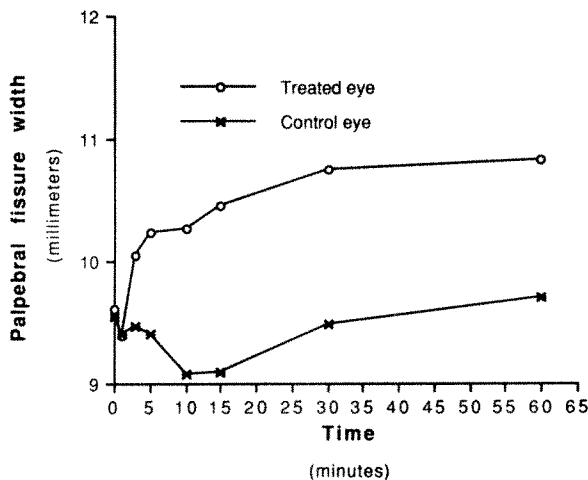


Fig. 4 (Munden and associates). Mean palpebral fissure responses of the control eye and the eye treated with topical 1% apraclonidine in ten normal subjects.

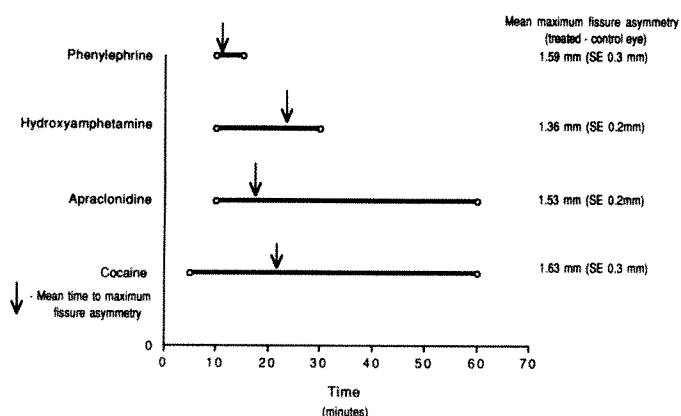


Fig. 5 (Munden and associates). The solid lines represent the time intervals for each drug in which there was no significant difference between the palpebral fissure asymmetry (mean of ten normal subjects) and the maximum fissure asymmetry attained after topical adrenergic drug treatment. The arrows mark the mean time for all ten volunteers when the fissure asymmetry reached maximum value. The optimum time for measuring fissure responses to these drugs appears to be from 15 to 30 minutes after administration. (SE indicates standard error.)

increase in fissure asymmetry. Neither age nor initial fissure size correlated with the maximum increase in fissure asymmetry.

To determine the best time to measure the drug effects, the measurements at each time interval were compared with the maximum fissure asymmetry for each drug. The time intervals during which there was no significant difference in fissure asymmetry from the maximum asymmetry were determined (Fig. 5).

The 15- to 30-minute time interval after drug administration appeared to be optimum for measurement; the direct-acting drugs had their effect somewhat sooner during the interval. The maximum drug effect was reached by 15 minutes in all volunteers after treatment with phenylephrine and by 30 minutes after treatment with hydroxyamphetamine or apraclonidine. The maximum effect of cocaine was seen in nine of ten patients within 30 minutes after treatment (Fig. 6). All drugs continued to show a diminished but significant effect at 60 minutes with 2.5% phenylephrine decreasing the most.

Discussion

Müller's muscle consists of sympathetically innervated smooth muscle fibers and acts together with the levator palpebrae superioris muscle to elevate the upper eyelid. Palpebral fissure widening after application of topical adrenergic drugs is often noted.

Our results show all four tested drugs were equivalent in their ability to increase the width of the palpebral fissure. The direct-acting adrenergic agents produced their effect more quickly than the indirect-acting drugs. The optimum time to measure the increase in fissure size appears to be 15 to 30 minutes after topical drug administration. Maximum increase in fissure width was achieved during this time period in 39 of 40 trials (97.5%). All drugs continued to show a significant but diminished effect at 60 minutes with 2.5% phenylephrine decreasing the most.

Our measured maximum increase in fissure

TABLE 2
MAXIMUM PALPEBRAL FISSURE ASYMMETRY AND TIME TO MAXIMUM ASYMMETRY IN TEN SUBJECTS*

DRUG	MAXIMUM PALPEBRAL FISSURE ASYMMETRY†		TIME TO MAXIMUM ASYMMETRY	
	MEAN (S.E.) (MM)	RANGE (MM)	MEAN (S.E.) (MIN)	RANGE (MIN)
Cocaine	1.63 (0.3)	0.65-2.85	21 (5)	5-60
Hydroxyamphetamine	1.36 (0.2)	0.60-2.55	23 (3)	10-30
Phenylephrine	1.59 (0.3)	0.60-2.35	11 (1)	3-15
Apraclonidine	1.53 (0.2)	0.45-3.00	18 (3)	5-30

*S.E. indicates standard error of the mean.

†Palpebral fissure asymmetry was determined for each subject by subtracting the palpebral fissure width of the treated eye from the width of the control eye.

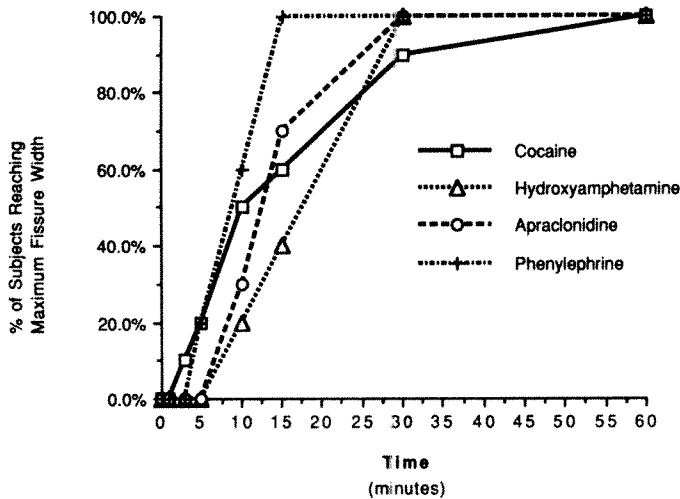


Fig. 6 (Munden and associates). Percentage of subjects who reached their maximum increase in palpebral fissure asymmetry for each drug at each time after drug administration. The maximum increase in fissure asymmetry for each drug was attained by 30 minutes in each subject with the exception of one subject in the cocaine group.

asymmetry in response to 2.5% phenylephrine (1.59 mm) and the mean time to the maximum (10.8 minutes) correlated closely with the results of Felt and Frueh.⁹ They found a mean maximum increase in fissure asymmetry of 1.3 mm with 2.5% phenylephrine and an average time to the maximum effect of 13 minutes.

The pharmacologic diagnosis of Horner's syndrome is usually based on pupillary reactions to topical cocaine.³⁻⁵ Pupil responses to topical hydroxyamphetamine can help localize the sympathetic lesion in Horner's syndrome to either a postganglionic or preganglionic location.^{6,7} Some patients, however, have pupils that react poorly to cocaine and hydroxyamphetamine. This may be caused in part by poor corneal penetration of topical drugs. Because of the sympathetic innervation of Müller's muscle and the ease with which topical drugs penetrate the conjunctiva, eyelid responses to topical cocaine and hydroxyamphetamine may be of use in the diagnosis and localization of Horner's syndrome.

The results of our study demonstrated an increase in palpebral fissure width in response to topical adrenergic drugs in normal volunteers. This information provides a basis for evaluating the function of Müller's muscle and the integrity of its sympathetic innervation. In a patient with blepharoptosis, a difference in the eyelid responses to bilaterally administered topical cocaine or hydroxyamphetamine could theoretically be used to help diagnose Horner's syndrome and localize the site of the sympathetic lesion.

References

1. Putterman, A. M., and Urist, M. J.: Müller muscle-conjunctiva resection. Technique for treatment of blepharoptosis. *Arch. Ophthalmol.* 93:619, 1975.
2. Robin, A. L., Pollack, I. P., and deFaller, J. M.: Effects of topical ALO 2145 (p-aminoclonidine hydrochloride) on the acute intraocular pressure rise after argon laser iridotomy. *Arch. Ophthalmol.* 105:1208, 1987.
3. Kardon, R. H., Denison, C. E., Brown, C. K., and Thompson, H. S.: Critical evaluation of the cocaine test in the diagnosis of Horner's syndrome. *Arch. Ophthalmol.* 108:384, 1990.
4. Friedman, J. R., Whiting, D. W., Kosmorsky, G. S., and Burde, R. M.: The cocaine test in normal patients. *Am. J. Ophthalmol.* 98:808, 1984.
5. Van der Wiel, H. L., and van Gijn, J.: The diagnosis of Horner's syndrome. Use and limitations of the cocaine test. *J. Neurol. Sci.* 73:311, 1986.
6. Cremer, S. A., Thompson, H. S., Digre, K. B., and Kardon, R. H.: Hydroxyamphetamine mydriasis in Horner's syndrome. *Am. J. Ophthalmol.* 110:71, 1990.
7. Thompson, H. S., and Mensher, J. H.: Adrenergic mydriasis in Horner's syndrome. The hydroxyamphetamine test for diagnosis of postganglionic defects. *Am. J. Ophthalmol.* 72:472, 1971.
8. Loewenfeld, I. E., and Rosskothorn, H. D.: Infra-red pupil camera. A new method for mass screening and clinical use. *Am. J. Ophthalmol.* 78:304, 1974.
9. Felt, D. P., and Frueh, B. R.: A pharmacologic study of the sympathetic eyelid tarsal muscles. *Ophthalmic Plast. Reconstr. Surg.* 4:15, 1988.

The Effect of Topical Antiglaucoma Drugs on the Results of High-Pass Resolution Perimetry

Lene M. Martin-Boglund, R.N., Adrienne Graves, Ph.D., and Peter Wanger, M.D.

We conducted a randomly assigned, double-masked, crossover study of the effects of betaxolol, epinephrine, pilocarpine, and timolol on the high-pass resolution perimetry results in normal subjects. The influence of topical administration of these intraocular pressure-reducing drugs was negligible, which confirmed the reliability of high-pass resolution perimetry results. The method seems appropriate for the diagnosis of glaucoma and the follow-up of patients with glaucoma.

SERIAL VISUAL FIELD examinations are essential for the diagnosis and management of glaucoma. The monitoring of antiglaucoma therapy is dependent upon the correct analysis of changes in the visual fields. High-pass resolution perimetry has been reported to be a sensitive test for optic nerve damage in glaucoma with low variability.^{1,3} The method has also given highly reproducible results in normal subjects.⁴ High-pass resolution threshold has been shown to correlate directly with retinal ganglion cell separation.² This proposal has been validated by comparison with other sophisticated techniques for demonstrating optic nerve damage. Wanger and Persson³ reported a good concordance between high-pass resolution perimetry findings and pattern-reversal electroretinograms. Airaksinen and associates⁵ found a good correlation between semiquantitative evaluation of retinal nerve fiber layer photographs and high-pass resolution perimetry results. Lindblom⁶ reported similar observations. A lin-

ear relationship has been observed when comparing reduction of the functional retinal area from laser photocoagulation and increase of the mean resolution threshold in patients with diabetes (B. Lindblom, unpublished data).

Miosis induced by pilocarpine has been shown to influence the visual field with differential light-sense perimetry.⁷⁻⁹ The decrease in sensitivity remained when compensating for the drug-induced myopia.⁷ We attempted to establish if and to what extent topical administration of intraocular pressure-reducing drugs would influence the results of high-pass resolution perimetry in normal subjects.

Subjects and Methods

The high-pass resolution perimetric system we used has been described previously.^{1,2} Briefly, it consisted of a personal computer with a second graphics card, which controlled the stimulus display monitor. The subjects in the study, eight men and seven women, were healthy volunteers, age-matched to typical patients with glaucoma (mean age, 66.7 ± 3 years; range, 61 to 72 years), with no history of ocular disease, no opacities of the optic media, normal intraocular pressure and fundus appearance, and best-corrected visual acuity of at least 20/20. They had had no previous experience with high-pass resolution perimetry. All subjects gave informed consent to participate in the study when the procedure and aims had been explained to them. The study was approved by the local ethical committee.

We instilled a single dose of betaxolol (0.5%), epinephrine (1%), pilocarpine (2%), or timolol (0.5%) in one eye and placebo in the other eye of all 15 studied subjects in a randomized, double-masked, crossover manner. Before the study and 90 minutes after the instillation, each subject was examined with subjective refraction, high-pass resolution perimetry, Goldmann tonometry, and pupil size measurement

Accepted for publication March 13, 1991.

From the Department of Ophthalmology, Sabbatsberg Hospital, Stockholm, Sweden (L. M. Martin-Boglund and Dr. Wanger); and Alcon Laboratories, Fort Worth, Texas (Dr. Graves). This study was supported by grants from the Stockholm County Council and Alcon Laboratories, Fort Worth, Texas.

Reprint requests to Lene Martin-Boglund, R.N., Department of Ophthalmology, Sabbatsberg Hospital, P.O. Box 6401, S-113 82 Stockholm, Sweden.

with a millimeter ruler. For each subject in the study this procedure was repeated on four occasions at approximately the same time of the day, with an interval of at least 48 hours. The eyes were tested in a random fashion.

Student's *t*-test and correlation tests were used for statistical analysis. A *P* value of less than .05 was considered statistically significant.

Results

The prestudy values for the 15 subjects (30 eyes) were the following: mean resolution threshold, 4.6 ± 0.6 dB; intraocular pressure, 15 ± 2.7 mm Hg; refraction, $+1 \pm 2.1$ diopters; and pupil diameter, 3.2 ± 0.5 mm. The mean resolution threshold from the first-examined eyes of each subject was 4.8 ± 0.5 dB and from the second-examined eyes 4.3 ± 0.7 dB (*P* = .031). The prestudy tests showed no statistically significant difference in mean resolution threshold between the right and left eyes (*P* = .27), when examined in random order.

No statistically significant difference in mean resolution threshold was found between the untreated and the treated eyes in any group (Table, Figs. 1 and 2). Betaxolol and timolol induced a significant reduction in intraocular pressure compared to prestudy values (*P* = .007 and *P* = .00016, respectively). No patient had an astigmatic refractive error of more than 1 diopter before or after drug instillation; thus, only spherical refraction was taken into account. No significant change in spherical refraction was observed. Pilocarpine induced a significant reduction in pupil diameter, from 3.2 to 1.6 mm (*P* < .00001), yet there was no significant change in mean resolution thresholds (*P* = .54).

Discussion

Visual field examinations are important in the diagnosis and management of glaucoma, and all factors that may influence the perimetric results have to be evaluated. We attempted to demonstrate the potential effects of topical antiglaucoma drugs on results from high-pass resolution perimetry.

In differential light-sense perimetry the threshold level in one single visual field location may show a variability of 10 dB.¹⁰ The high-pass resolution perimetric technique has shown low variability both in normal subjects and patients with glaucoma.^{3,4,11} There is a small learning effect, however, between the first and second examination in normal subjects, subjects suspected of having glaucoma, and patients with glaucoma,¹² and a still smaller effect, although not statistically significant, over a longer period.⁴ We observed a statistically significant decrease in mean resolution threshold values of 0.5 dB between the first- and second-examined eyes (*P* = .031), which indicated a learning effect.

In this single-dose study, we observed no statistically significant effects of the tested antiglaucoma drugs on the mean resolution threshold. The timolol-treated eyes performed slightly worse compared to the control eyes (mean resolution threshold, 4.5 ± 0.6 dB compared with 4.2 ± 0.6 dB), but this difference was not statistically significant (*P* = .18). In patients with glaucoma a statistically significant reduction in differential light sensitivity has been reported after treatment with timolol.¹³

We observed a significant intraocular pressure decrease with betaxolol and timolol when compared to the prestudy values. There was no correlation between intraocular pressure level

TABLE
EFFECTS OF TESTED DRUGS ON STUDY FACTORS*

	PRESTUDY	PLACEBO	BETAXOLOL		EPINEPHRINE		PILOCARPINE		TIMOLOL	
			TREATED	PLACEBO	TREATED	PLACEBO	TREATED	PLACEBO	TREATED	PLACEBO
Mean resolution threshold (dB)	4.6 ± 0.6	4.3 ± 0.6	4.2 ± 0.7	4.1 ± 0.6	4.4 ± 0.7	4.4 ± 0.7	4.5 ± 0.4	4.4 ± 0.5	4.4 ± 0.6	4.2 ± 0.6
Intraocular pressure (mmHg)	15 ± 2.7	14 ± 2.8	12 ± 3	14 ± 2.9	15 ± 2.8	14 ± 2.6	13 ± 3.2	14 ± 3.2	11 ± 2.3	13 ± 2.7
Refraction (diopters)	$+1.0 \pm 2.1$	$+1.0 \pm 2.2$	$+1.1 \pm 2$	$+1.1 \pm 2.3$	$+1 \pm 2$	$+1 \pm 2.2$	$+1 \pm 2.2$	$+1.1 \pm 2$	$+1 \pm 2.2$	$+1.1 \pm 2.1$
Pupil diameter (mm)	3.2 ± 0.5	3.1 ± 0.4	3.2 ± 0.4	3.2 ± 0.4	3.7 ± 1.0	3.3 ± 0.5	1.6 ± 0.7	3.2 ± 0.4	3 ± 0.4	3 ± 0.3

*Values given are mean \pm standard deviation.

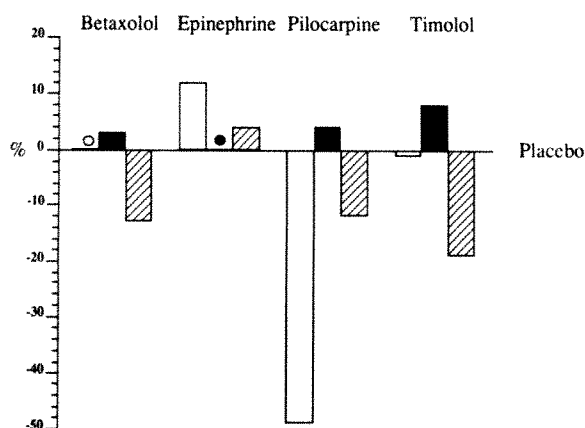


Fig. 1 (Martin-Boglund, Graves, and Wanger). Mean percentage change in relation to placebo for each drug. Open bars indicate pupil size; filled bars indicate mean resolution threshold; shaded bars indicate intraocular pressure; open circle indicates no change in pupil size; and filled circle indicates no change in mean resolution threshold.

and mean resolution threshold values in this group of normal subjects. None of the drugs induced any significant change in refraction, presumably because of the age of the subjects (range, 61 to 72 years).

Campbell and Gubisch¹⁴ determined the eye's optimal optical performance by recording the light reflected from the bright image of a thin line projected on the fundus through an artificial pupil in front of a cycloplegic eye. They derived line-spread profiles from Fourier-analyzed modulation transfer functions. The most narrow profile, which indicated optimal spatial resolution, was observed when the pupil diameter was 1.5 to 2.5 mm. If pupil size was reduced much below this, the visual performance deteriorated because of diffraction, decreased illumination, or both.

McCluskey and associates⁷ found a statistically significant correlation between percentage change in pupillary area and visual field by pilocarpine-induced miosis with Goldmann perimetry. Mikelberg and associates⁸ used Octopus perimetry (program G1) to demonstrate a statistical relationship between the change in pupil diameter and mean sensitivity. Lindemuth and associates⁹ reported a 0.67-dB sensitivity decrease in pilocarpine-treated eyes compared to baseline visual fields with the Humphrey Field Analyzer 30-2.

In our study, a pilocarpine-induced reduction in pupil diameter from 3.2 to 1.6 mm did not significantly change the mean resolution

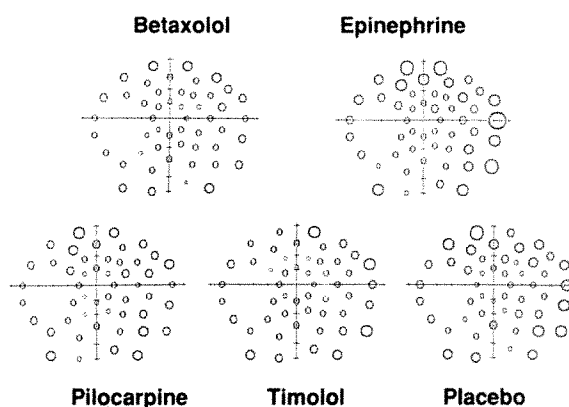


Fig. 2 (Martin-Boglund, Graves, and Wanger). Graphic printouts of the visual fields from one of the subjects. The visual fields were practically identical regardless of the drug given.

threshold value. This finding is in agreement with the results from modulation transfer measurements. Thus, direct comparisons between differential light-sense measurement and high-pass resolution perimetry may be less relevant, because of the entirely different physiologic properties of the stimuli. To what extent reduction of pupil diameter much below 1.6 mm would influence the resolution perimetry could not be determined from our study.

Our findings in this single-dose study show that the influence of topical administration of intraocular pressure-reducing drugs on the high-pass resolution threshold is negligible. High-pass resolution perimetry may be useful for follow-up of patients with glaucoma with the previously described learning effect taken into account.^{4,12}

References

1. Frisén, L.: A computer-graphics visual field screener using high-pass spatial frequency resolution targets and multiple feedback devices. *Doc. Ophthalmol. Proc. Ser.* 49:441, 1987.
2. ———: High-pass resolution targets in peripheral vision. *Ophthalmology* 94:1104, 1987.
3. Wanger, P., and Persson, H. E.: Pattern-reversal electroretinograms and high-pass resolution perimetry in suspected or early glaucoma. *Ophthalmology* 94:1098, 1987.
4. Martin-Boglund, L. M., and Wanger, P.: The influence of feed-back devices, learning and cheating on the results of high-pass resolution perimetry. In Heijl, A. (ed.): *Perimetry Update. Proceedings of the*

Eighth International Perimetric Society Meeting 1988-1989. Amstelveen, Kugler & Ghedini Publishers, 1989, pp. 393-398.

5. Airaksinen, P. J., Tuulonen, A., Välimäki, J., and Alanko, H. I.: Retinal nerve fiber layer abnormalities and high-pass resolution perimetry. *Acta Ophthalmol.* 68:687, 1990.

6. Lindblom, B.: High-pass resolution perimetry. A new method for the early detection of visual field defects. *Int. J. Ophthalmol.* 7:33, 1990.

7. McCluskey, D. J., Douglas, J. P., O'Connor, P. S., Story, K., Ivy, L. M., and Harvey, J. S.: The effect of pilocarpine on the visual field in normals. *Ophthalmology* 93:843, 1986.

8. Mikelberg, F. S., Drance, S. M., Schulzer, M., and Wijsman, K.: The effect of miosis on visual field indices. *Doc. Ophthalmol. Proc. Ser.* 49:645, 1986.

9. Lindenmuth, K. A., Skuta, G. L., Rabbani, R., and Musch, D. C.: Effects of pupillary constriction on automated perimetry in normal eyes. *Ophthalmology* 96:1298, 1989.

10. Heijl, A., Lindgren, G., and Olsson, J.: Normal variability of static perimetric threshold values

across the central visual field. *Arch. Ophthalmol.* 105:1544, 1987.

11. Douglas, G. R., Drance, S. M., Mikelberg, F. S., Schulzer, M., and Wijsman, K.: Variability of the Frisén ring perimeter. In Heijl, A. (ed.): *Perimetry Update. Proceedings of the Eighth International Perimetric Society Meeting 1988-1989.* Amstelveen, Kugler & Ghedini Publishers, 1989, pp. 197-198.

12. Drance, S. M., Douglas, G. R., Schulzer, M., and Wijsman, C. S.: The learning effect of the Frisén high pass resolution perimeter. In Heijl, A. (ed.): *Perimetry Update. Proceedings of the Eighth International Perimetric Society Meeting 1988-1989.* Amstelveen, Kugler & Ghedini Publishers, 1989, pp. 199-201.

13. Drance, S. M., and Flammer, J.: Some effect of antiglaucoma drugs on visual function. In Drance, S. M., and Neufeld, A. H. (eds.): *Glaucoma. Applied Pharmacology in Medical Treatment.* Orlando, Florida, Grune & Stratton, 1984, pp. 569-576.

14. Campbell, F. W., and Gubisch, R. W.: Optical quality of the human eye. *J. Physiol.* 186:558, 1966.

OPHTHALMIC MINIATURE

Hedonia Hypothesis: *noun*, a hypothesis in neuropsychology holding that stress and other "negative hedonic states" tend to increase a subject's eyeblink frequency, and that "positive hedonic states," such as contentment and pleasure, tend to decrease eyeblink frequency. Also called *hedonia-blink hypothesis*. "In the blink of an eyelash, [Joseph J.] Tecce puts to work his hedonia hypothesis. . . . [He] has trained his. . . eyes on two statesmen caught in the crucible of world events, President Bush and. . . Saddam Hussein, who are locked in an eyeball-to-eyeball confrontation in the Persian Gulf. If Tecce's data are accurate, Saddam will blink first in the war of nerves" (*The Boston Herald*).

Anne H. Soukhanov, *The Atlantic*
February 1991, p. 96

Pseudophakic Pupillary-Block Glaucoma in Children

R. B. Vajpayee, M.D., S. K. Angra, M.D., J. S. Titiyal, M.D.,
Y. R. Sharma, M.D., and V. K. Chhabra, M.Sc.

We studied 16 children, ranging in age between 3 and 8 years, who had posterior chamber intraocular lens implantation and developed inflammatory pupillary-block glaucoma. Prophylactic peripheral iridectomy had not been performed in any of the eyes. The patients were treated medically, and YAG laser iridotomy was performed successfully one week after initial control of intraocular pressure. Of 16 eyes in which intraocular pressure remained uncontrolled, trabeculectomy was necessary in three eyes and irreversible glaucomatous visual loss occurred in two eyes. Our data demonstrate the need for stringent and more frequent postoperative follow-up of children after intraocular lens implantation, especially during the first four postoperative weeks. Careful long-term follow-up for treatment after cataract is mandatory to prevent development of amblyopia.

INTRAOCULAR LENS implantation in monocular children with aphakia has advantages compared with the use of spectacles and contact lenses.¹⁻⁵ For example, eyes with intraocular lenses have better postoperative visual acuity.¹ Although the long-term results remain unknown and secondary membranes, intraocular lens precipitates, and postpseudophakos membrane formation are common complications of intraocular lens implantation in children, the procedure is likely to be used more frequently.¹ We studied 16 children with pupillary-block glaucoma after extracapsular cataract extraction and posterior chamber intraocular lens implantation.

Patients and Methods

Between September 1988 and January 1990, pseudophakic glaucoma was diagnosed in 16 pediatric patients examined at our institution. We reviewed the admission records of these patients, including complete preoperative assessment records, operative notes, and immediate postoperative records. Of the 16 implanted posterior chamber intraocular lenses, 14 had polypropylene haptics and two were single-piece, polymethylmethacrylate. We performed extracapsular cataract extraction and posterior chamber intraocular lens implantation in all patients. Peripheral iridectomy was not performed. All patients had uneventful postoperative courses and were discharged from the hospital on the third or fourth postoperative day. Topical antibiotic corticosteroid eyedrops and ointment were given routinely for all patients. Postoperative visual acuity at the time of discharge ranged between 20/20 and 20/200 (Table).

In all eyes at the initial examination, slit-lamp biomicroscopy disclosed moderate stromal edema of the cornea, shallow anterior chamber, iris bombé, anterior chamber flare and cells, and seclusio pupillae caused by iridopseudophakos synechiae. Exudative deposits on the anterior surface of the intraocular lenses were also seen. The posterior capsule was intact in all eyes. The fundus could not be clearly visualized in any of the eyes because of hazy media. Intraocular pressure by applanation tonometry ranged between 30 and 60 mm Hg (mean, 38.43 mm Hg; standard deviation, ± 8.27 mm Hg). These findings suggested a diagnosis of inflammatory pupillary-block glaucoma. All patients were readmitted, and initial treatment included the following: topical 0.1% dexamethasone eyedrops four times daily; timolol eyedrops 0.25% twice daily; 1% tropicamide eyedrops twice daily; systemic oral acetazolamide, 10 mg/kg of body weight per day; and prednisolone, 1.5 mg/kg of body weight per day. After intraocular pressure was con-

Accepted for publication March 6, 1991.

From the Dr. R. P. Centre for Ophthalmic Sciences, All India Institute of Medical Sciences, Ansari Nagar, New Delhi, India.

Reprint requests to R. B. Vajpayee, M.D., Dr. R. P. Centre for Ophthalmic Sciences, All India Institute of Medical Sciences, Ansari Nagar, New Delhi 110029, India.

TABLE
DATA ON 16 CHILDREN AFTER EXTRACAPSULAR CATARACT EXTRACTION AND POSTERIOR CHAMBER
INTRAOCULAR LENS IMPLANTATION*

CASE NO., AGE (YRS), SEX	TYPE OF CATARACT	TYPE OF INTRAOCULAR LENS	POST- OPERATIVE VISUAL ACUITY	INTRA- OCULAR PRESSURE (MM HG)	VISUAL ACUITY AFTER GLAUCOMA	TYPE OF THERAPY	RESPONSE	ALTERNATIVE THERAPY	FINAL VISUAL ACUITY AFTER YAG CAPSULOTOMY
1, 8, M	Developmental	[†] Polymethacrylate	20/200	34	CF	Medical	Positive	—	10/200
2, 6, M	Traumatic	3-piece	20/60	38	20/200	Medical	Positive	—	20/40
3, 3, M	Traumatic	3-piece	20/80	NA	NA	Medical	Positive	—	20/200
4, 5, M	Traumatic	3-piece	20/30	60	NA	Medical	Negative	Trabeculectomy	20/200
5, 6, M	Developmental	3-piece	20/30	32	20/200	Medical	Positive	—	20/20
6, 7, M	Developmental	3-piece	20/30	40	20/200	Medical	Positive	—	20/30
7, 8, M	Traumatic	3-piece	20/60	38	CF	Medical	Positive	—	20/40
8, 6, M	Developmental	3-piece	20/30	36	20/200	Medical	Positive	—	20/20
9, 5, M	Developmental	3-piece	20/40	30	20/200	Medical	Positive	—	20/40
10, 4, M	Traumatic	3-piece	20/60	52	NA	Medical	Negative	Trabeculectomy	20/200
11, 7, M	Traumatic	3-piece	20/60	36	20/100	Medical	Positive	—	20/60
12, 8, M	Developmental	3-piece	20/60	38	20/200	Medical	Negative	Trabeculectomy	20/60
13, 7, M	Traumatic	[†] Polymethacrylate	20/30	30	20/100	Medical	Positive	—	20/30
14, 6, M	Developmental	3-piece	20/40	34	20/200	Medical	Positive	—	20/30
15, 5, M	Traumatic	3-piece	20/60	NA	NA	Medical	Positive	—	20/80
16, 6, M	Traumatic	3-piece	20/40	40	20/200	Medical	Positive	—	20/30

*NA indicates not available because the patient was not cooperative, and CF indicates counting fingers.

[†]1-piece.

trolled initially, YAG laser iridotomy was performed within two to three days in all eyes. Initial YAG iridotomy failed in all eyes, but repeat YAG iridotomy one week later was performed successfully in all eyes. In eyes with uncontrolled intraocular pressure after medical therapy and YAG iridotomy, trabeculectomy was performed immediately after inflammation was controlled. All patients were examined twice weekly for a minimum of three months after being discharged from the hospital.

Results

All 16 children were boys, ranging in age between 3 and 8 years (mean \pm standard deviation, 6.06 ± 1.43 years). Of 16 eyes, nine had traumatic cataracts, and seven had unilateral developmental cataracts (Table). None of the eyes had preexisting glaucoma.

The duration between intraocular lens implantation and initial manifestation of pseudophakic pupillary-block glaucoma varied between 12 and 16 days (mean \pm standard deviation, 14 ± 2 days). Initial visual acuity

with increased intraocular pressure ranged between 20/200 and counting fingers in 11 eyes. Because of patient noncooperation, visual acuity could not be recorded in the remaining five eyes. Medical therapy controlled inflammation and intraocular pressure in 13 eyes. YAG laser iridotomy attempted initially on the third or fourth postoperative day failed in all the eyes; however, it was performed successfully one week after attaining medical control of intraocular inflammation and increased intraocular pressure.

In three eyes, the inflammation was controlled with medical therapy and YAG laser iridotomy was performed successfully, but intraocular pressure remained increased. In all of these eyes, the irides were apposed to the anterior surface of the intraocular lenses, and extensive synechial closure of the angle was noted. Trabeculectomy in these eyes resulted in control of intraocular pressure. None of the eyes had any recurrence of glaucoma during a three-month follow-up period at our clinic. During this period all eyes developed a thick postpseudophakos membrane, which was managed by YAG laser membranectomy.

Final visual acuity after YAG capsulotomy

recorded at the three-month follow-up visit showed improvement in 13 eyes (Table). Of the three eyes that showed no visual acuity improvement better than 20/200, one had amblyopia. In the remaining two eyes, glaucomatous optic atrophy accounted for the visual loss.

Discussion

Pseudophakic pupillary-block glaucoma has been reported with all types of intraocular lenses.⁶⁻⁸ Pupillary block is relatively more common after anterior chamber intraocular lens implantation than after posterior chamber implantation.^{7,9,10} This complication has been described usually in adult age groups.^{8,11,12} All of our patients were in the pediatric age group, between 3 and 8 years of age.

The exact pathogenesis of pupillary-block glaucoma with posterior chamber lenses is not clear and may be related to a number of factors, including alteration of angle anatomy, forward movement of vitreous caused by zonular or capsular disruption, and preexisting angle closure.⁸ None of our patients had preexisting glaucoma, and the posterior capsule was intact in all of the eyes. Zonular disruption was not suspected in any of the eyes because there was no evidence of pupillary plugging by vitreous.

Postoperative severe inflammation has rarely caused pupillary-block glaucoma after intraocular lens insertion.^{7,13} In our series, all eyes had moderate to severe degrees of uveal inflammation, which resulted in iridopseudophakos synechiae and subsequent pupillary-block glaucoma. Inflammation in the postoperative period after cataract surgery and intraocular lens implantation may be related to trauma,¹⁴⁻¹⁶ residual lens matter,^{14,15} breakdown of blood-aqueous barrier caused by mechanical damage,^{16,18} and foreign body-type response to implant material.¹⁹ Also, glaucoma after cataract surgery is common in young children and can result from a variety of mechanisms, including inflammation.²⁰⁻²³ In the eyes in our series, pupillary block was attributed to postoperative inflammation, which resulted in apposition of the iris to the intraocular lens. We have seldom noted this phenomenon in adults after posterior chamber intraocular lens implantation, which is performed more frequently.

Topical miotic therapy has been advocated in noninflammatory pseudophakic pupillary-block glaucoma.⁸ Use of miotics in pupillary-

block glaucoma caused by inflammation may actually aggravate the condition.⁷ Medical therapy with topical corticosteroids, mydriatics and cycloplegics, and antiglaucoma drugs resulted in control of intraocular pressure in 13 of 16 patients (81%). Absence or closure of surgical iridectomies also predisposes eyes with intraocular lenses to pupillary block.¹¹⁻¹³ Concomitant surgical iridectomies were not performed in any of our patients. Regardless of the mechanism, once the pupillary block occurs, presence of a patent peripheral iridectomy as an alternative channel for aqueous flow is of paramount importance.^{7,8} In all of our patients, successful YAG laser iridotomy was performed, but in three eyes trabeculectomy was also performed because intraocular pressure remained uncontrolled with medical therapy and YAG laser iridotomy. To prevent corneal damage, filtration surgery by trabeculectomy should be performed.^{24,25}

Our data suggest a more conservative and guarded approach to intraocular lens implantation in children. The irreversible visual loss in two eyes highlights the need for stringent and more frequent postoperative follow-up in pediatric patients with intraocular lenses, especially during the first four postoperative weeks. Careful long-term follow-up for treatment after cataract is vital to avert development of possible rapid amblyopia. Also, the frequent development of postpseudophakos membranes suggests that primary capsulotomy at the time of lens implantation might be preferable. Severe adverse consequences of pupillary block suggest that a routine peripheral iridectomy in pediatric intraocular lens procedures should be considered. Preoperative use of topical prostaglandin inhibitors may also be potentially useful. The development of severe inflammation with increased intraocular pressure in the early postoperative period suggests that secondary intraocular lens procedures may be a better choice for children's eyes.

References

1. Hiles, D. A.: Visual acuities of monocular IOL and non IOL aphakic children. *Ophthalmology* 87:1296, 1980.
2. Binkhorst, C. D., and Gobin, M. H.: Injuries to the eye with lens opacity in young children. *Ophthalmologica* 148:169, 1964.
3. Rubinstein, K.: Management of unilateral aphakia. *Br. Orthop. J.* 17:82, 1960.

4. von Noorden, G. K., Ryan, S. J., and Maumenee, A. E.: Management of congenital cataracts. *Trans. Am. Acad. Ophthalmol. Otolaryngol.* 74:352, 1970.
5. Hiles, D. A.: Need for intraocular lens implantation in children. *Ophthalmic Surg.* 8:162, 1977.
6. Bresnick, G. H.: Eyes containing anterior chamber acrylic implants. *Arch. Ophthalmol.* 82:726, 1969.
7. Werner, D., and Kaback, M.: Pseudophakic pupillary block glaucoma. *Br. J. Ophthalmol.* 61:329, 1977.
8. Samples, J. R., Bellows, R., Rosenquist, R. C., Hutchinson, B. T., Fine, I. H., and Van Buskirk, E. M.: Pupillary block with posterior chamber intraocular lenses. *Arch. Ophthalmol.* 105:335, 1987.
9. Van Buskirk, E. M.: Pupillary block after intraocular lens implantation. *Am. J. Ophthalmol.* 95:55, 1983.
10. Shrader, C. E., Belcher, C. D., Thomas, J. V., Simmons, R. J., and Murphy, E. B.: Pupillary and iridovitreous block in pseudophakic eyes. *Ophthalmology* 91:831, 1984.
11. Willis, D. A., Steward, R. H., and Kimbrough, R. L.: Pupillary block associated with posterior chamber lenses. *Ophthalmic Surg.* 16:108, 1985.
12. Neveh-Floman, N., Rosner, M., and Blumenthal, M.: Pseudophakic pupillary block glaucoma with posterior-chamber intraocular lens. *Glaucoma* 7:262, 1985.
13. Ferayorni, J. F.: Intraocular lenses and secondary glaucoma. A retrospective study. *Ann. Ophthalmol.* 10:1447, 1978.
14. Tomey, K. F., and Traverso, C. E.: Neodymium-YAG laser posterior capsulotomy for the treatment of aphakic and pseudophakic pupillary block. *Am. J. Ophthalmol.* 104:502, 1987.
15. Apple, D. J., Mamalis, N., Lofteld, K., Googe, J. M., Novak, L. C., Dolores, N. K., Brady, S. E., and Olson, R. J.: Complications of intraocular lenses. A historical and histopathological review. *Surv. Ophthalmol.* 29:1, 1984.
16. Smith, R. E.: Inflammation after cataract surgery. *Am. J. Ophthalmol.* 102:788, 1986.
17. Dulaney, D. D.: IOL and iris erosion. *Am. Intraocular Implant. Soc. J.* 208:120, 1978.
18. Sanders, D. R., Kraff, M. C., Lieberman, H. L., Peymann, G. A., and Tarabisky, S.: Breakdown and reestablishment of blood-aqueous barrier with implant surgery. *Arch. Ophthalmol.* 100:588, 1982.
19. Sawa, M., Sakanishi, Y., and Shimizu, H.: Fluorophotometric study of anterior segment barrier functions after extracapsular cataract extraction and posterior chamber intraocular lens implantation. *Am. J. Ophthalmol.* 97:197, 1984.
20. Galin, M. A.: Causes of implant inflammation. In Rosen, E. S., Haining, W. M., and Arnott, F. (eds.): *Intraocular Lens Implantation*. St. Louis, C. V. Mosby, 1984, pp. 563-565.
21. Epstein, D. L.: Lens-induced glaucoma. In Chandler, P. A., and Grant, W. M. (eds.): *Glaucoma*, ed. 2. Philadelphia, Lea & Febiger, 1979, pp. 216-223.
22. Walton, D. S.: Glaucoma secondary to operation for childhood cataract. In Chandler, P. A., and Grant, W. M. (eds.): *Glaucoma*, ed. 2. Philadelphia, Lea & Febiger, 1979, pp. 363-368.
23. Phelps, C. D., and Arafat, N. I.: Open-angle glaucoma following surgery for congenital cataracts. *Arch. Ophthalmol.* 95:1985, 1977.
24. Keech, R. V., Tongue, A. C., and Scott, W. E.: Complications after surgery for congenital and infantile cataracts. *Am. J. Ophthalmol.* 108:136, 1989.
25. Simcoe, C. W.: Retaining devices for protection of corneal endothelium. *Am. Intraocular Implant. Soc. J.* 5:234, 1979.

Leptomeningeal Dissemination of Optic Pathway Gliomas in Three Children

Carol S. Bruggers, M.D., Henry S. Friedman, M.D., Peter C. Phillips, M.D.,
M. David Wiener, M.D., Beverly Hockenberger, B.H.S., W. Jerry Oakes, M.D.,
and Edward G. Buckley, M.D.

We treated three children with optic pathway gliomas who had progressive disease associated with metastatic spread to the leptomeninges. One patient had radiographic resolution of leptomeningeal disease after treatment with intravenous carmustine and oral mercaptopurine but died of progressive pulmonary fibrosis. The second patient was treated with intravenous thiotepa, and the leptomeningeal disease remained stable. The third patient was treated with intravenous vincristine sulfate, cyclophosphamide, cisplatin, and etoposide and had a significant size reduction of the leptomeningeal lesion. Although leptomeningeal dissemination is a seemingly rare event, it is important that all children with optic pathway gliomas be considered for this possibility, particularly after the onset of new, atypical neurologic symptoms.

OPTIC PATHWAY GLIOMAS, rare tumors comprising 1% to 5% of childhood intracranial neoplasms, occur primarily in the first two decades of life.^{1,2} The clinical course can be variable and often unpredictable, ranging from stability of both vision and tumor for long periods of time to total blindness and death resulting from local tumor invasion. Because of this, contro-

versy exists regarding the optimal therapy for optic pathway gliomas. Proposed therapeutic options include observation alone, surgery, radiation therapy, or chemotherapy. Clinical features influencing the choice of therapy include the severity of symptoms, precise location and extent of tumor, functional impairment, and age of the patient.

Although most optic pathway gliomas follow an indolent course, accelerated local progression and, rarely, metastatic spread may occur. We treated three children with optic pathway gliomas who had progressive disease associated with metastatic spread to the leptomeninges.

Case Reports

Case 1

In October 1986, an 8-year-old boy had visual loss in his right eye, and amblyopia was diagnosed. Progressive visual deterioration occurred despite patching of his left eye. In March 1987, a cranial computed tomographic scan disclosed a 3-cm enhancing, multiloculated, cystic mass of the posterior optic chiasm, which extended to the anterior base of the brain. An exploratory right frontoparietal craniotomy was performed, and biopsy of the mass disclosed a pilocytic astrocytoma. The child was treated with radiotherapy to the residual mass, receiving 5,075 cGy (in daily fractions of 175 cGy).

In August 1987, the patient had episodic visual disturbance and cognitive disorientation. Cranial computed tomography again disclosed the enhancing suprasellar mass, ventricular enlargement, and new subarachnoid tumor dissemination (Fig. 1). Cerebrospinal fluid analysis demonstrated a protein level of 364 mg/dl and clusters of cytologically benign astrocytes, consistent with dissemination of a

Accepted for publication March 15, 1991.

From the Division of Hematology/Oncology, Department of Pediatrics (Drs. Bruggers and Friedman and Ms. Hockenberger), Department of Radiology (Dr. Wiener), Division of Neurosurgery (Dr. Oakes), and Department of Ophthalmology (Dr. Buckley), Duke University Medical Center, Durham, North Carolina; and Department of Pediatric Neuro-oncology, Johns Hopkins Hospital, Baltimore, Maryland (Dr. Phillips).

Reprint requests to Carol S. Bruggers, M.D., P.O. Box 2916, Pediatric Hematology-Oncology, Duke University Medical Center, Durham, NC 27710.

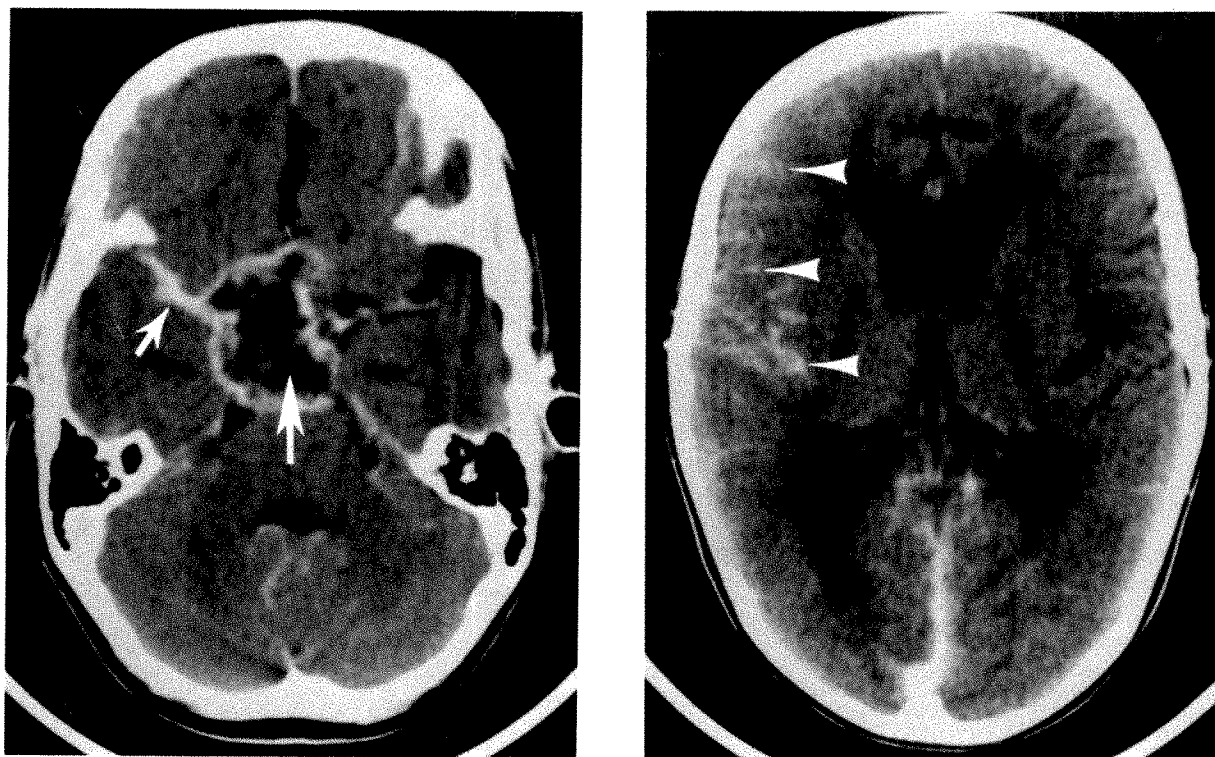


Fig. 1 (Bruggers and associates). Case 1. Noncontiguous images from contrast-enhanced cranial computed tomographic scan show enhancing cystic suprasellar mass (large arrow) with contiguous extension into the right sylvian cistern (small arrow) and throughout the right hemispheric sulci (arrowheads).

mature glioma. A ventriculoperitoneal shunt was placed.

The patient was then treated with oral 6 mercaptopurine (200 mg/m² on Days 1, 2, and 3) and a single dose of intravenous carmustine (200 mg/m²) given at six-week intervals. A cranial computed tomographic scan performed after two courses of medication disclosed a decrease in both tumor size and subarachnoid dissemination. After four courses of medication, a cranial computed tomographic scan disclosed further decrease in the tumor size and resolution of leptomeningeal disease. The patient developed progressive pulmonary fibrosis and cor pulmonale, however, which required continued intervention with furosemide and oxygen and discontinuation of systemic chemotherapy. In March 1988, a cranial computed tomographic scan disclosed a slight decrease in the tumor mass size and no evidence of subarachnoid dissemination. Unfortunately, the patient died of progressive pulmonary fibrosis and severe cor pulmonale.

Case 2

A 14-week-old girl was admitted to her local hospital for examination because of failure to

thrive, developmental delay, emesis, and dehydration. On the third day in the hospital, she developed a full, nontense anterior fontanelle and rotatory nystagmus. A cranial ultrasound disclosed a solid suprasellar mass with mild ventriculomegaly. Contrast-enhanced magnetic resonance imaging disclosed a 5 × 4 × 3-cm enhancing tumor in the suprasellar cistern, multiple punctate areas of enhancement on the surface of the pons, and spinal subarachnoid drop metastases (Fig. 2). Results of bone marrow aspirate, bone marrow biopsy, and abdominal ultrasound showed no evidence of tumor. Cerebrospinal fluid analysis disclosed the following values: protein, 142 mg/dl; glucose, 51 mg/dl; red blood cell count, 30 cells/μl; white blood cell count, 1 cell/μl and a differential of 100% lymphocytes. Isolated atypical cells were also present. The patient was transferred to Duke University Medical Center for further examination and treatment.

Upon arrival at Duke University Medical Center, the patient was alert with the following vital signs and growth variables: heart rate, 140 beats per minute; blood pressure, 110/68 mm Hg; respirations, 32 per minute; weight, 4.67 kg (tenth percentile); height, 61.5 cm (60th per-

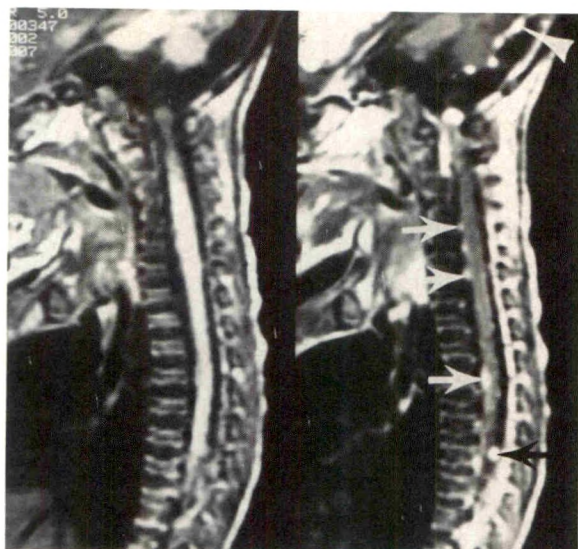


Fig. 2 (Bruggers and associates). Case 2. Composite T₁-weighted (TR = 500 msec, TE = 20 msec) mid-sagittal magnetic resonance images of the cervico-thoracic spine with (right) and without (left) gadopentetate dimeglumine contrast enhancement. The spinal cord is irregularly widened on the noncontrast image (left) with multiple abnormal enhancing lesions in the cranial (arrowhead) and spinal (arrows) subarachnoid space consistent with metastases.

centile); and head circumference, 41 cm (75th percentile). The head and neck examination showed a full, nonbulging anterior fontanelle, mild paralysis of vertical gaze, and diminished extraocular movements with pendular nystagmus. Cardiovascular examination disclosed an irregular heart rate and periodic hypotension. Neurologic abnormalities included weakness of the oculomotor, trochlear, and abducent nerves, and pendular nystagmus. Ophthalmic examination disclosed complete clinical blindness.

She was admitted to the pediatric intensive care unit because of cardiac instability and treated with dexamethasone, 0.35 mg/kg of body weight per day, and fluid restriction. Subtotal resection of the huge suprasellar mass was performed. The mass originated at the optic chiasm, encased the vessels of the circle of Willis, and impinged bilaterally on the medial aspects of the temporal lobes. The right optic nerve was enlarged. There were no apparent metastatic lesions on the surface of the brain. Final pathologic examination disclosed pilocytic astrocytoma. Postoperative complications included diabetes insipidus responsive to desmopressin acetate, periodic hypothalamic autonomic instability, panhypopituitarism treated with corticosteroid and thyroid hormone re-

placement, and subsequent development of subdural fluid collections requiring placement of a shunt.

A regimen of intravenous thiopeta, 3.25 mg/kg of body weight, at three-week intervals was begun. Six weeks later a cranial computed tomographic scan disclosed no change in the suprasellar mass when compared with postoperative scans. Myelography disclosed persistent subarachnoid drop metastases. After careful consideration of the multiple aspects of the infant's problem, her parents decided against further therapeutic intervention. As of November 1990, the patient remained alive, although she was severely developmentally and neurologically compromised.

Case 3

A 2-year-old boy was examined at Johns Hopkins University Medical Center in September 1988 for a two-month history of roving conjugate ocular movements and a one-month history of bumping into objects. A cranial computed tomographic scan disclosed an extremely large hypothalamic, retrochiasmal multicystic tumor with extensions along the optic radiations. He had no other symptoms.

Physical examination showed bilateral optic atrophy, diminished visual acuity, a left visual field defect, right lateral gaze preference, roving nystagmoid pattern of conjugate ocular movement that was most prominent on right lateral gaze, upbeat nystagmus, and counter-clockwise rotatory nystagmus. Plantar stimulation evoked a flexor response on the left and withdrawal on the right.

On Sept. 26, 1988, the patient underwent needle aspiration biopsy and decompression of the cysts. Pathologic examination disclosed a mature astrocytoma. Cerebrospinal fluid obtained at that time was suggestive of tumor cells, and subsequent myelography demonstrated an extensive intradural extramedullary lesion extending dorsally from the lower cervical region to the lower thoracic region.

The patient was given chemotherapy with intravenous vincristine sulfate and cyclophosphamide alternating with cisplatin and etoposide. There was a greater than 50% reduction in the size of the leptomeningeal tumor in response to this chemotherapy.

Discussion

Optic pathway gliomas are most frequently diagnosed during the first 20 years of life.

Although the tumor may develop anywhere within the optic pathway, most involve the optic nerve or the optic chiasm.^{1,2} Furthermore, 20% to 60% of patients with optic pathway gliomas also have neurofibromatosis.¹⁻⁵ The clinical signs and symptoms at diagnosis include visual impairment, strabismus, proptosis, optic atrophy with or without swelling of the optic disk, and an afferent pupillary defect. Increased intracranial pressure may also be present and result in headache, nausea, emesis, and paralysis of vertical gaze. Hypothalamic involvement may be indicated by diabetes insipidus or precocious puberty. Extensive tumors may also be noted with diencephalic syndrome manifested as hyperactivity, increased alertness, pallor, and emaciation despite seemingly adequate caloric intake.

When reviewing the long-term survival data from several different studies concerning optic pathway gliomas, it becomes clear that considerable variation in clinical outcome exists.^{1,3,6-8} Involvement of the optic chiasm, hydrocephalus, and increased age at diagnosis are among the factors associated with a less favorable outcome.^{6,7} Flickenger, Torres, and Deutsch² described 36 pediatric patients with optic pathway gliomas treated between 1965 and 1983. Actuarial survival of patients with gliomas confined to the optic nerve was 100% (seven patients) at five, ten, and 15 years after diagnosis. Actuarial survival of patients with tumors involving the optic chiasm was 93% (28 of 30 patients), 90% (27 of 30 patients), and 90% (27 of 30 patients) at five, ten, and 15 years, respectively. Imes and Hoyt⁷ reported an 82% (23 of 28 patients) 15-year survival rate from optic chiasmal tumors. Bilgic and associates⁸ reported that six of 16 patients (37.5%) with intracranial optic pathway gliomas were alive eight years after diagnosis. Although visual acuity remained stable in the survivors, only one patient, who underwent biopsy followed by radiation therapy, had full vision. Hypothalamic involvement is also associated with a poorer outcome. In a review of published reports with a 20-year follow-up, Alvord and Lofton⁶ reported that the mortality of patients with untreated, uncomplicated optic chiasmal tumors was 47% (20 of 43 patients died) as compared with 91% (31 of 34 patients died) if the hypothalamus was also involved.

Other reports have described children with clinically aggressive optic pathway gliomas despite displaying histologic features consistent with low-grade lesions. De Keizer and associates⁹ described a 3-year-old boy with neurofibromatosis who had a large juvenile pilocytic

astrocytoma involving the optic nerve and the globe with intraocular seeding of the vitreous. Although the ocular portion of the tumor was composed of a mature astrocytoma, there were small islands of grade three astrocytoma in the optic canal. Civitello and associates¹⁰ described 162 patients with low-grade gliomas; six patients (3.7%) had leptomeningeal tumor spread. Only one of these patients had an optic pathway glioma, which involved the optic chiasm. This patient had dissemination after local radiation therapy and died within two years of leptomeningeal dissemination. Kocks and associates¹¹ described a 10-year-old girl with a juvenile pilocytic astrocytoma of the optic chiasm, initially treated with radiation therapy. Six years later enlargement of the primary tumor produced further visual deterioration. Within three years she had lumbar metastases, with the histologic characteristics of the tumor identical to those of the primary tumor. Trigg, Swanson, and Letellier¹² described a 3½-year-old boy with a glioma involving the optic chiasm and left optic nerve who was treated with primary radiation therapy after placement of a ventriculoperitoneal shunt. After six months the tumor progressed, and he was treated with intravenous vincristine and dactinomycin. Four months later, he had ascites after the development of cerebrospinal fluid and peritoneal seeding with malignant cells.

No obvious features of a low-grade optic pathway astrocytoma are totally predictive of biologically aggressive behavior. A worse prognosis has been described in infants with optic pathway gliomas as compared with older children. Kanamori and associates¹³ described seven pediatric patients with optic pathway gliomas and noted that after a follow-up period exceeding eight years, five of seven children with childhood gliomas were alive, compared with only one of four patients with infantile gliomas. One of the patients with infantile gliomas died of progressive tumor, one of infection, and one of hypothalamic crises.

Alvord and Lofton⁶ devised a mathematic model describing the growth kinetics of optic pathway gliomas based on time to recurrence of disease. They concluded that these histologically benign gliomas of the optic pathway had a variable growth rate ranging along a continuum from a simple logarithmic rate to a decelerating growth rate. Upon microscopic examination, local infiltration of the leptomeninges by tumor cells, with sparing of the dura mater, has been well described in astrocytomas involving the globe and optic nerves, as well as the chiasm and adjacent structures, although the clinical

prognosis is more favorable in the globe and optic nerves.¹⁴

The ability to detect neoplastic cells in cerebrospinal fluid in patients with benign intracranial gliomas before surgery has been demonstrated. Wilkins and Odom¹⁵ reported a 25% incidence (22 of 87 patients) of neoplastic cells from benign intracranial gliomas in the cerebrospinal fluid before surgery without a significant increase after surgery. Surgery did not seem to play a role in tumor dissemination in our three patients, because one of the children had widespread disease before surgery, one had a needle aspiration biopsy only, and the third patient had an open biopsy followed by radiation therapy before dissemination. It remains unclear why in a small percentage of patients, leptomeningeal dissemination of low-grade astrocytomas occurs.

Most optic pathway gliomas in children have an indolent clinical course, with radiotherapy^{1-3,16} and more recently chemotherapy¹⁷ improving the duration and quality of survival. Despite low-grade histologic features, however, occasionally optic pathway gliomas behave in a biologically aggressive fashion, with development of leptomeningeal metastases and death. Although leptomeningeal dissemination of gliomas generally has a poor prognosis, three of the six patients described by Civitello and associates¹⁰ were alive after multiagent systemic chemotherapy with or without radiation therapy. One of these patients was still alive more than three years after the diagnosis of leptomeningeal dissemination from the spinal glioma.

With improved radiologic diagnostic capabilities, earlier detection of leptomeningeal spread may be possible and may impact significantly upon treatment planning and overall prognosis. It is important that all children with optic pathway tumors be considered for this possibility, particularly patients who have large, infiltrating chiasmal tumors and patients with new, atypical neurologic symptoms. Increased awareness of this potential problem should prompt a more extensive examination in this subgroup of patients with optic pathway gliomas, including cranial and spinal gadolinium-enhanced magnetic resonance imaging and cerebrospinal fluid examination.

References

1. Wong, J. C. Y., Uhl, V., Wara, W. M., and Sheline, G. E.: Optic gliomas. A reanalysis of the University of California, San Francisco experience. *Cancer* 60:1847, 1987.
2. Flickenger, J. C., Torres, C., and Deutsch, M.: Management of low-grade gliomas of the optic nerve and chiasm. *Cancer* 61:635, 1988.
3. Weiss, L., Sagerman, R. H., King, G. A., Chung, C. T., and Dubowy, R. L.: Controversy in the management of optic nerve glioma. *Cancer* 59:1000, 1987.
4. Easley, J. D., Scharf, L., Chou, J. L., and Riccardi, V. M.: Controversy in the management of optic pathway gliomas. *Neurofibromatosis* 1:248, 1988.
5. Duffner, P. K., and Cohen, M. E.: Isolated optic nerve gliomas in children with and without neurofibromatosis. *Neurofibromatosis* 1:201, 1988.
6. Alvord, E. C., and Lofton, S.: Gliomas of the optic nerve of chiasm. Outcome by patient's age, tumor site and treatment. *J. Neurosurg.* 68:85, 1988.
7. Imes, R. K., and Hoyt, W. F.: Childhood chiasmal gliomas. Update on the fate of patients in the 1969 San Francisco study. *Prog. Exp. Tumor Res.* 30:108, 1987.
8. Bilgic, S., Erbenli, A., Tinaztepe, B., and Onol, B.: Optic glioma of childhood. Clinical, histopathological, and histochemical observations. *Br. J. Ophthalmol.* 73:832, 1989.
9. de Keizer, R. J. W., de Wolff-Rouendaal, D., Bots, G. T. A. M., Thomeer, R. T. W. M., Brouwer, O. F., and Vielvoye, G. J.: Optic glioma with intraocular tumor and seeding in a child with neurofibromatosis. *Am. J. Ophthalmol.* 108:717, 1989.
10. Civitello, L. A., Packer, R. J., Rorke, L. B., Siegel, P. A., Sutton, L. N., and Schut, L.: Leptomeningeal dissemination of low grade gliomas in childhood. *Neurology* 38:562, 1988.
11. Kocks, W., Kalff, R., Reinhardt, V., Grote, W., and Hilke, J.: Spinal metastasis of pilocytic astrocytoma of the chiasma opticum. *Child Nerv. Syst.* 5:18, 1989.
12. Trigg, M. E., Swanson, J. D., and Letellier, M. A.: Metastasis of an optic glioma through a ventriculoperitoneal shunt. *Cancer* 52:599, 1983.
13. Kanamori, M., Shibuya, M., Yoshida, J., Takayasu, M., and Kageyama, N.: Long-term follow-up of patients with optic glioma. *Child Nerv. Syst.* 1:72, 1985.
14. Borit, A., and Richardson, E. P., Jr.: The biological and clinical behavior of pilocytic astrocytomas of the optic pathways. *Brain* 105:16, 1982.
15. Wilkins, R. H., and Odom, G. L.: Cytological changes in cerebrospinal fluid associated with resections of intracranial neoplasms. *J. Neurosurg.* 25:24, 1966.
16. Kovalic, J. J., Grigsby, P. W., Shepard, M. J., Fineberg, B. B., and Thomas, P. R.: Radiation therapy for gliomas of the optic nerve and chiasm. *Int. J. Radiat. Oncol. Biol. Phys.* 18:927, 1990.
17. Packer, R. J., Sutton, L. N., Bilaniuk, L. T., Radcliffe, J., Rosenstock, J. G., Seigel, K. R., Bunin, G. R., Savino, P. J., Bruce, D. A., and Schut, L.: Treatment of chiasmal/hypothalamic gliomas of childhood with chemotherapy. An update. *Ann. Neurol.* 23:79, 1988.

Optic Nerve Sheath Decompression for the Treatment of Progressive Nonarteritic Ischemic Optic Neuropathy

Thomas C. Spoor, M.D., Michael J. Wilkinson, M.D., and John M. Ramocki, M.D.

We performed optic nerve sheath decompression on four patients (five eyes) with visual loss secondary to nonarteritic anterior ischemic optic neuropathy. Four of the five eyes had marked improvement in visual function after the operation. Optic nerve sheath decompression is an effective treatment for patients with nonarteritic ischemic optic neuropathy and progressive visual loss.

NONARTERITIC ISCHEMIC OPTIC NEUROPATHY causes mild to marked visual loss and occurs typically in older patients, who have sudden, painless loss of visual function, an afferent pupillary defect, and optic disk edema.¹ For most patients, the visual loss is sudden and stable; however, in a small percentage of patients, ranging from 4% to 30%, the visual loss may progress within six weeks.²⁻⁶ Spontaneous subsequent visual improvement is rare.

Recently, optic nerve sheath decompression has been advocated for the treatment of progressive nonarteritic ischemic optic neuropathy.⁷ The effectiveness of this treatment has raised some controversy.^{8,9} We treated four patients (five eyes), who had progressive nonarteritic ischemic optic neuropathy, by optic nerve sheath decompression. Four of the five eyes showed improved visual acuity and expansion of the visual fields; one eye with nonprogressive total loss of vision showed no significant postoperative improvement. Our results support the previous findings that optic nerve sheath decompression improves visual loss caused by progressive nonarteritic ischemic optic neuropathy, a disorder previously without a successful therapy.

Accepted for publication March 14, 1991.

From the Kresge Eye Institute, Wayne State University, Detroit, Michigan.

Reprint requests to Thomas C. Spoor, M.D., F.A.C.S., Kresge Eye Institute, Wayne State University, 4717 St. Antoine, Detroit, MI 48201.

Patients and Methods

The diagnosis of nonarteritic ischemic optic neuropathy was made after a complete neuro-ophthalmic examination. After progressive loss of visual function occurred and was documented, all patients underwent optic nerve sheath decompression with lysis of presumed arachnoid adhesions by one of us (T.C.S.) with a previously described surgical technique.¹⁰

All patients showed decreased central visual acuity and visual field deficits associated with optic disk edema and peripapillary nerve fiber layer hemorrhages. No inflammatory reaction occurred in the eyes.

All patients had normal Westergren sedimentation rates (< 30 mm/hour) and normal results of computed tomography of the head and orbits. Preoperative standardized echography with the 30-degree test demonstrated fluid within the optic nerve sheath in two patients. No patient had previous visual dysfunction or neurologic dysfunction consistent with inflammatory optic neuritis, demyelination, or pseudotumor cerebri.

Case Reports

Case 1

A 66-year-old man, who had a history of hypertension and a myocardial infarction one year previously, noted a sudden, painless loss of vision in his left eye for one week. He had a large relative afferent pupillary defect in the left eye. Visual acuity was R.E.: 20/20 and L.E.: hand motions. Intraocular pressure was R.E.: 16 mm Hg and L.E.: 14 mm Hg. Ophthalmoscopy disclosed slight pallor of the left optic disk with mild swelling of the peripapillary nerve fiber layer. The right optic disk appeared normal. The patient was given intravenous megadose corticosteroids for three days without res-

olution. Results of a temporal artery biopsy were negative. Results of computed tomography, spinal fluid pressure, serologic studies, Westergren sedimentation rate, and blood cell count were all normal. His vision remained stable until January 1989, at which time he noted a decrease in vision of his right eye. Visual acuity in the right eye decreased to 20/25, and an inferonasal visual field defect sparing fixation was noted.

On follow-up examination one week later, visual acuity decreased to 20/50 in the right eye and remained hand motions in the left eye. A relative afferent pupillary defect persisted in the left eye. The anterior chamber was quiet. Ophthalmoscopy disclosed an edematous optic disk with hemorrhages in the right eye and a pale, atrophic optic disk in the left eye. The inferonasal visual field defect in the right eye had progressed and became markedly constricted (Fig. 1).

Results of serologic tests and complete blood cell count were normal. Westergren sedimentation rate was 18 mm/hour. Results of computed tomography of the head and orbit were negative, and a lumbar puncture disclosed clear, colorless cerebrospinal fluid with normal pressure, protein, and glucose levels. No pleocytosis was noted. Standardized echography with the 30-degree test disclosed normal fluid accumulation in the right optic nerve sheath.

Three days later, a right optic nerve sheath decompression with lysis of arachnoid adhesions was performed. After the operation, visual acuity improved to 20/25 in the right eye and remained hand motions in the left eye. Goldmann visual field testing showed expansion of the right visual field (Fig. 2). Visual acuity and visual fields have remained stable for 18 months.

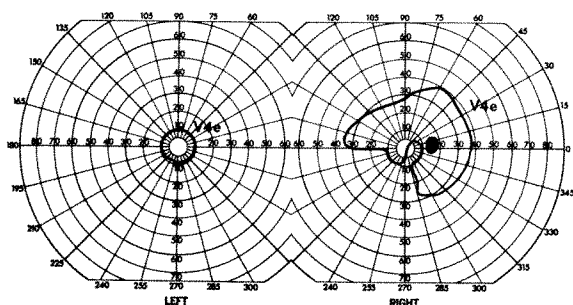


Fig. 1 (Spoor, Wilkinson, and Ramocki). Case 1. Preoperative visual field with visual acuity of 20/50 in the right eye.

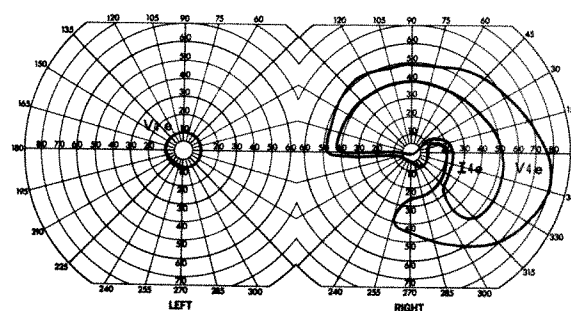


Fig. 2 (Spoor, Wilkinson, and Ramocki). Case 1. Postoperative visual field with visual acuity of 20/25 in the right eye.

Case 2

A 72-year-old man noted progressive, painless visual loss for one month. He had been examined by his ophthalmologist approximately two months before this visual loss with best-corrected visual acuity of 20/20 in both eyes. The patient had had hypertension and coronary artery disease.

Visual acuity was R.E.: 20/200 and L.E.: counting fingers at 2 feet with a relative afferent pupillary defect on the left side. Visual fields demonstrated marked constriction and a central scotoma in the right eye and peripheral constriction and a relative central scotoma in the left eye (Fig. 3). Intraocular pressure was normal. No ocular inflammation was noted. Ophthalmoscopy disclosed marked optic disk edema with peripapillary nerve fiber layer hemorrhages in both eyes. Results of serologic tests and complete blood cell count were normal. Westergren sedimentation rate was 24 mm/hour. Results of computed tomography and lumbar puncture including intracranial pressure were also normal. Results of a left temporal artery biopsy were negative.

Optic nerve sheath decompression was performed on the left eye. One week after the operation, visual acuity improved to 20/60, and the visual field expanded (Fig. 4). Visual acuity and visual fields have remained stable for four months. Visual acuity improved to 20/25 in the unoperated on eye, and the visual field expanded (Fig. 4).

Case 3

A 62-year-old man had bilateral loss of vision after coronary artery bypass surgery. The patient had had hypertension, coronary artery disease, and diabetes mellitus. Visual acuity was R.E.: 20/30 and L.E.: no light perception. The right pupil reacted sluggishly to light,

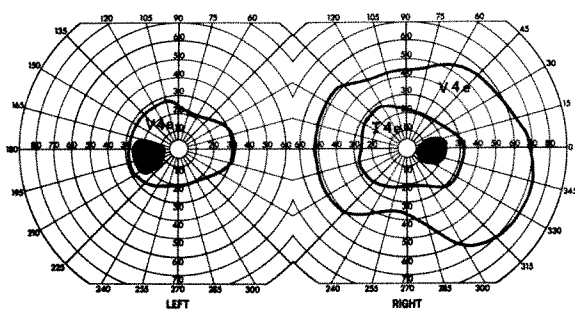


Fig. 3 (Spoor, Wilkinson, and Ramocki). Case 2. Preoperative visual field with visual acuity of R.E.: 20/50 and L.E.: counting fingers at 2 feet.

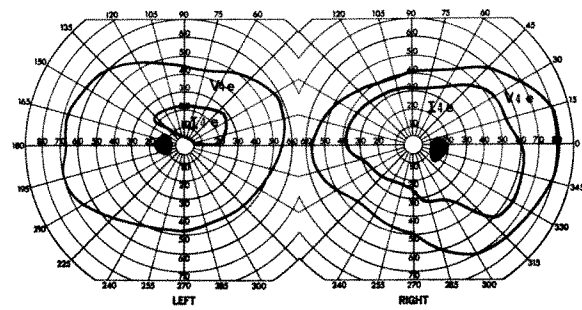


Fig. 4 (Spoor, Wilkinson, and Ramocki). Case 2. Postoperative visual field with visual acuity of R.E.: 20/25 and L.E.: 20/100.

and the left pupil was amaurotic. The patient had bilateral pseudophakia. Ophthalmoscopy showed pallor and optic disk edema in both eyes. An inferior altitudinal visual field defect was noted in the right eye. One week later, visual acuity decreased to 20/400 in the right eye. The visual field was markedly contracted (Fig. 5). Visual acuity in the left eye remained no light perception. The left pupil was amaurotic, and the right pupil reacted poorly to light. The anterior segment was not inflamed. Ophthalmoscopy disclosed bilateral pallor and disk swelling with nerve fiber layer hemorrhages. Results of computed tomography, lumbar punctures, and the Westergren sedimentation rate (25 mm/hour) were normal.

The patient underwent bilateral optic nerve sheath decompression with lysis of arachnoid adhesions. One day postoperatively, visual acuity improved to R.E.: 20/50 and L.E.: light perception. The right visual field improved significantly. One month after the operation, visual acuity was 20/25 in the right eye. An inferonasal defect was noted on the visual field (Fig.

6). Visual acuity in the left eye remained light perception.

Case 4

A 61-year-old woman noted sudden, painless visual loss in her right eye that progressed during one week to severe visual loss. The patient had had hypertension and diet-controlled diabetes mellitus. On successive examinations, visual acuity decreased from 20/25 to 20/80 to hand motions in the right eye. Visual acuity in the left eye remained 20/25. The anterior segment was normal in both eyes, the right optic disk was edematous, and the left optic disk was normal. Visual field examination showed a dense central scotoma in the right eye (Fig. 7). Results of computed tomography of the head and orbits and lumbar puncture were negative. Results of serologic tests and complete blood cell count were normal. Westergren sedimentation rate was 27 mm/hour. Standardized echography with the 30-degree test demonstrated fluid in the right optic nerve sheath.

A right optic nerve sheath decompression

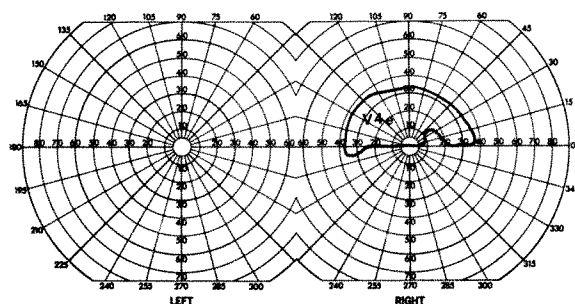


Fig. 5 (Spoor, Wilkinson, and Ramocki). Case 3. Preoperative visual field with visual acuity of 20/400 in the right eye.

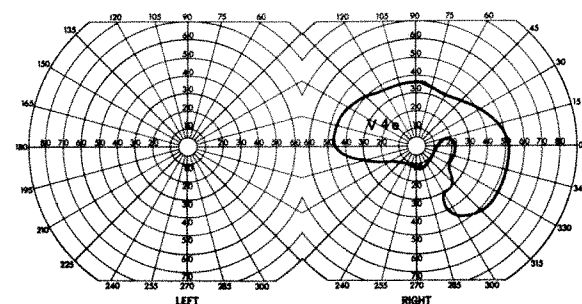


Fig. 6 (Spoor, Wilkinson, and Ramocki). Case 3. Postoperative visual field with visual acuity of 20/25 in the right eye.

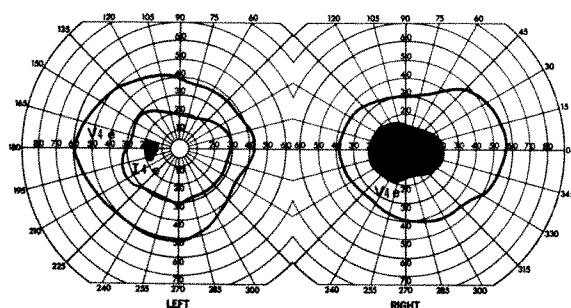


Fig. 7 (Spoor, Wilkinson, and Ramocki). Case 4. Preoperative visual field with visual acuity of hand motions in the right eye.

was performed. One month after the operation, visual acuity improved to 20/25 in the right eye with marked improvement of the visual field (Fig. 8). This improvement has remained stable for five months.

Results

All four eyes undergoing optic nerve sheath decompression for progressive nonarteritic ischemic optic neuropathy had significant improvement in visual function (Table). Visual improvement has remained stable for five to 30 months after optic nerve sheath decompression (average, 14 months). Visual acuity in one eye with sudden and total visual loss improved to light perception after optic nerve sheath decompression. We do not consider this improvement significant or the visual loss progressive.

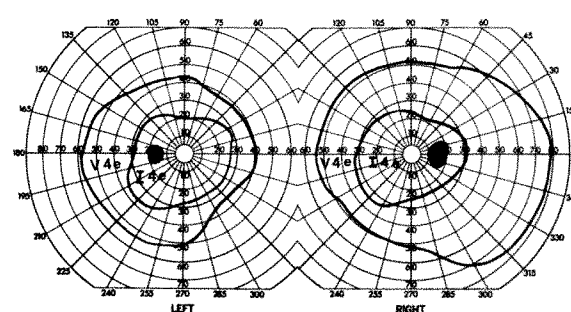


Fig. 8 (Spoor, Wilkinson, and Ramocki). Case 4. Postoperative visual field with visual acuity of 20/25 in the right eye.

Standardized echography of the retrobulbar optic nerve was performed in two patients. Both had intrasheath fluid and positive results of the 30-degree test. At surgery, these nerve sheaths appeared distended, and a moderate amount of cerebrospinal fluid was drained upon incision of the nerve sheath. No hemorrhage was noted in any optic nerve sheath at the time of decompression.

Discussion

Optic nerve sheath decompression reverses visual dysfunction caused by acute and chronic papilledema, presumably by increasing vascular perfusion and decreasing axoplasmic stasis.^{10,11} We performed optic nerve sheath decompression with lysis of arachnoid adhesions on five eyes of four patients with progressive se-

TABLE
CHARACTERISTICS OF PATIENTS UNDERGOING OPTIC NERVE SHEATH DECOMPRESSION FOR NONARTERITIC ISCHEMIC OPTIC NEUROPATHY*

CASE NO., AGE (YRS), SEX	EYE	INITIAL VISUAL ACUITY	PREOPERATIVE		POSTOPERATIVE		ONSET TO SURGERY
			VISUAL ACUITY	VISUAL FIELD	VISUAL ACUITY	VISUAL FIELD	
1, 66, M	R.E.	20/25	20/50	Inferior altitudinal defect	20/25	Inferonasal defect, fixation spared	10 days
2, 72, M	L.E.	20/100	CF at 2 ft	Central scotoma, peripheral constriction	20/100	Relative central scotoma	1 month
	R.E.	20/200	20/200	Relative central, peripheral constriction	20/25	Full	Nonoperated on fellow eye
3, 62, M	R.E.	20/30	20/400	Inferior altitudinal, fixation involved	20/25	Inferonasal defect, fixation spared	1 week
	L.E.	NLP	NLP	NP	LP	NP	1 week
4, 61, F	R.E.	20/25	HM	Central scotoma	20/25	Full	1 week

*CF indicates counting fingers; NLP indicates no light perception; NP indicates not performed; LP indicates light perception; and HM indicates hand motions.

vere visual loss secondary to nonarteritic ischemic optic neuropathy. Our results correlate well with the data of Sergott and associates.⁷ Four of the five eyes had improved visual acuity and expansion of their visual fields after optic nerve sheath decompression and lysis of arachnoid adhesions. These results are markedly better than the natural course of progressive nonarteritic ischemic optic neuropathy.¹⁻³

Visual acuity improved within one week and continued to improve for several months before stabilizing. Surgical intervention need not be emergent, since visual improvement after the operation was noted by us as well as by Sergott and associates⁷ even when performed 30 days after the onset of visual symptoms. Repeated neuro-ophthalmic examination, including visual acuity and visual field testing, should be done weekly after the initial diagnosis of nonarteritic ischemic optic neuropathy to detect progression of the disease. If progressive visual loss ensues, optic nerve sheath decompression should be considered.

We believe that optic nerve sheath decompression provides a rational therapy for progressive nonarteritic ischemic optic neuropathy. This procedure addresses the relationship between relative ischemia and axoplasmic transport stasis by decreasing axonal swelling at the optic nerve head that would otherwise potentiate axonal ischemia and nerve fiber attrition.

No other treatment has been shown to be effective in the management of this disease. Visual outcome in patients with progressive nonarteritic ischemic neuropathy has been poor.¹⁻³ Optic nerve sheath decompression with lysis of arachnoid adhesions is an effective treatment for progressive nonarteritic ischemic optic neuropathy as demonstrated by both our results and those of Sergott and associates.⁷ We believe the decrease of perineural pressure and the return of axoplasmic flow at the optic disk decreases optic disk swelling and prevents further axonal attrition, which breaks the edema-ischemia cycle that probably causes the progressive nature of this disease.

The patient in Case 2, with bilateral nonarteritic ischemic optic neuropathy, showed dramatic improvement in visual function in the right eye after optic nerve sheath decompression in the more severely affected left eye. Visual acuity increased from 20/60 to 20/25, and the visual field improved markedly (Table). Our other patients had either unilateral disease and a normal contralateral eye (Case 4), optic atrophy from previous arteritic ischemic optic neu-

ropathy (Case 1), or total visual loss in the contralateral eye (Case 3). Sergott and associates⁷ described similar improvement in the non-operated on eyes in two of seven patients with bilateral ischemic optic neuropathy. It is not known whether this is because of decreased perineural pressure in the fellow eye or increased blood flow.

Our data support that previously published by Sergott and associates,⁷ which demonstrated improved visual function after optic nerve sheath decompression with lysis of arachnoid adhesions for progressive nonarteritic ischemic optic neuropathy. Optic nerve sheath decompression should be considered when nonarteritic ischemic optic neuropathy is diagnosed in a patient with progressive visual dysfunction.

References

1. Boghen, D. R., and Glaser, J. S.: Ischemic optic neuropathy. The clinical profile and natural history. *Brain* 98:689, 1975.
2. Kline, L. B.: Progression of visual defects in ischemic optic neuropathy. *Am. J. Ophthalmol.* 106:199, 1988.
3. Borchert, M., and Lessell, S.: Progressive and recurrent nonarteritic anterior ischemic optic neuropathy. *Am. J. Ophthalmol.* 106:443, 1988.
4. Ellenberger, C., Keltner, J. L., and Burde, R. M.: Acute optic neuropathy in older patients. *Arch. Ophthalmol.* 28:182, 1973.
5. Boghen, D. R., and Glaser, J. S.: Ischemic optic neuropathy. The clinical profile and natural history. *Brain* 98:689, 1975.
6. Kline, L. B.: Progression of visual defects in ischemic optic neuropathy. *Am. J. Ophthalmol.* 106:199, 1988.
7. Sergott, R. C., Cohen, M. S., Bosley, T. M., and Savino, P. J.: Optic nerve decompression may improve the progressive form of nonarteritic ischemic optic neuropathy. *Arch. Ophthalmol.* 107:1743, 1989.
8. Hayreh, S. S.: The role of optic nerve sheath fenestration in management of nonarteritic ischemic optic neuropathy (letter to the editor). *Arch. Ophthalmol.* 108:1063, 1990.
9. Wilson, W. D.: Does optic nerve sheath decompression help progressive ischemic optic neuropathy? (letter to the editor). *Arch. Ophthalmol.* 108:1065, 1990.
10. Brouman, N. D., Spoor, T. C., and Ramocki, J. M.: Optic nerve sheath decompression for pseudotumor cerebri. *Arch. Ophthalmol.* 106:1378, 1988.
11. Sergott, R. C., Savino, P. J., and Bosley, T. M.: Modified optic nerve sheath decompression provides long-term visual improvement in pseudotumor cerebri. *Arch. Ophthalmol.* 106:1384, 1988.

Magnetic Resonance Imaging Signs of Optic Nerve Gliomas in Neurofibromatosis 1

Richard K. Imes, M.D., and William F. Hoyt, M.D.

We reviewed the magnetic resonance images of four children with neurofibromatosis 1 and orbital optic gliomas. The images showed double-intensity tubular thickening characteristic of perineural arachnoidal gliomatosis, elongation of the nerves, and downward kinking of the nerves in the midorbit. We believe these findings typify the orbital gliomas in patients with this disease.

IN PATIENTS WITH GLIOMAS of the optic pathway, the first neuroradiologic sign recognized as specific for neurofibromatosis 1 was bilaterality.¹ The second sign was a fusiform tumor of high signal intensity surrounding a core of lower signal intensity on T₂-weighted magnetic resonance images.² Such a radiologic appearance corresponds to the histopathologic pattern of perineural arachnoidal gliomatosis, which is a special feature of orbital gliomas in neurofibromatosis 1.³

We studied additional features of orbital gliomas in neurofibromatosis 1 seen on magnetic resonance images, including double-intensity tubular thickening, elongation, and downward kinking of the nerves.

Patients and Methods

We reviewed the magnetic resonance images of four patients with neurofibromatosis 1 who

were examined either in the Neuro-ophthalmology Unit at the University of California, San Francisco, or in the eye clinic at Oakland Naval Hospital. The images of all four patients showed evidence of chiasmal and bilateral orbital optic gliomas. Three patients had multiple café au lait spots, and T₂-weighted magnetic resonance images of their brains showed scattered foci of high signal intensity. The fourth patient had no signs of neurofibromatosis 1 other than a glioma involving the chiasm and both optic nerves. Magnetic resonance imaging was performed on various scanners without contrast enhancement.

Case Reports

Case 1

A 16-year-old girl with multiple café au lait spots developed hydrocephalus caused by a cerebellar pilocytic astrocytoma. She had undergone surgery for partial removal of an optic glioma from her right orbit. She had visual acuity of 20/25 and loss of the superior visual field in her left eye.

A T₁-weighted axial magnetic resonance image showed tortuous tubular thickening of both optic nerves (Fig. 1). Anteriorly, the right optic nerve was absent, and the left optic nerve had an area of low signal intensity around a core of higher signal intensity. The left optic nerve was elongated and bent downward sharply in the midorbit (Fig. 2). A T₂-weighted image showed a midline cerebellar tumor, dilated lateral ventricles, and bilateral thickening of the orbital optic nerves (Fig. 3). Anteriorly, the left optic nerve had a zone of high signal intensity around a core of low signal intensity. Removal of the cerebellar tumor provided relief of the hydrocephalus, but both optic nerves continued to show zones of high signal intensity surrounding a core of low signal intensity (Fig. 4).

Accepted for publication March 6, 1991.

From the Department of Ophthalmology, Naval Hospital, Oakland, California (Dr. Imes); and Neuro-ophthalmology Unit, Departments of Neurological Surgery, Neurology, and Ophthalmology, School of Medicine, University of California, San Francisco, California (Dr. Hoyt). The opinions and assertions expressed herein are those of the authors and are not to be construed as official or as necessarily reflecting the views of the Department of the Navy or of the Naval Service at large.

Reprint requests to William F. Hoyt, M.D., Department of Neurological Surgery, c/o Editorial Office, 1360 Ninth Ave., Ste. 210, San Francisco, CA 94122.

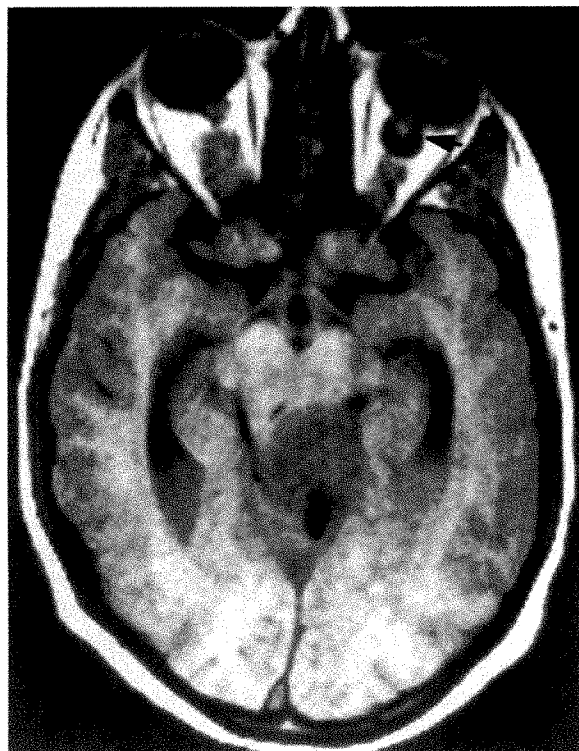


Fig. 1 (Imes and Hoyt). Case 1. T_1 -weighted axial magnetic resonance image. Anteriorly in the left optic nerve, an area of low signal intensity surrounds a core of higher signal intensity (arrow).

Case 2

An 8-year-old girl had multiple café au lait spots and a plexiform neuroma of the right upper eyelid at the initial examination. The child was adopted, and her family history was unknown. In the right eye, visual acuity was 20/20 with a full visual field and a normal optic disk; in the left eye, visual acuity was counting fingers with a constricted visual field and a pale optic disk.

T_1 -weighted sagittal magnetic resonance images of the left optic nerve showed tubular thickening (Fig. 5). The nerve was elongated and bent downward. An area of low signal intensity surrounded a core of higher intensity. On a T_2 -weighted axial image, the left optic nerve appeared kinked (Fig. 6). Anteriorly, an area of high signal intensity surrounded a core of lower signal intensity.

Case 3

A 21-month-old girl with no family history of neurofibromatosis was examined for multiple café au lait spots. She was able to fix and follow

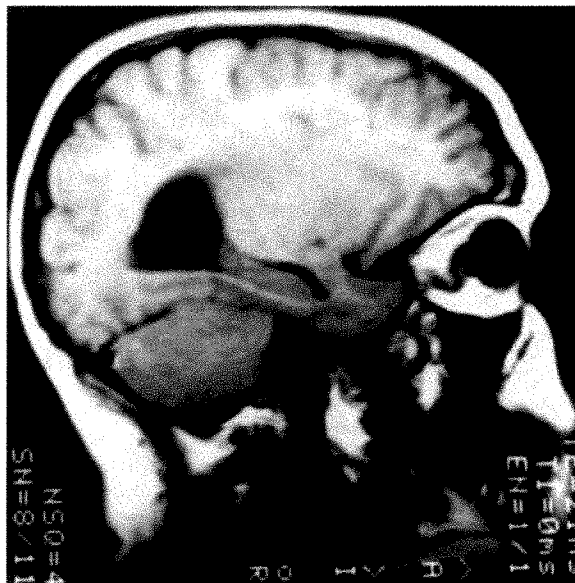


Fig. 2 (Imes and Hoyt). Case 1. T_1 -weighted sagittal magnetic resonance image of the left orbit. The optic nerve is elongated and bent downward in the mid-orbit.

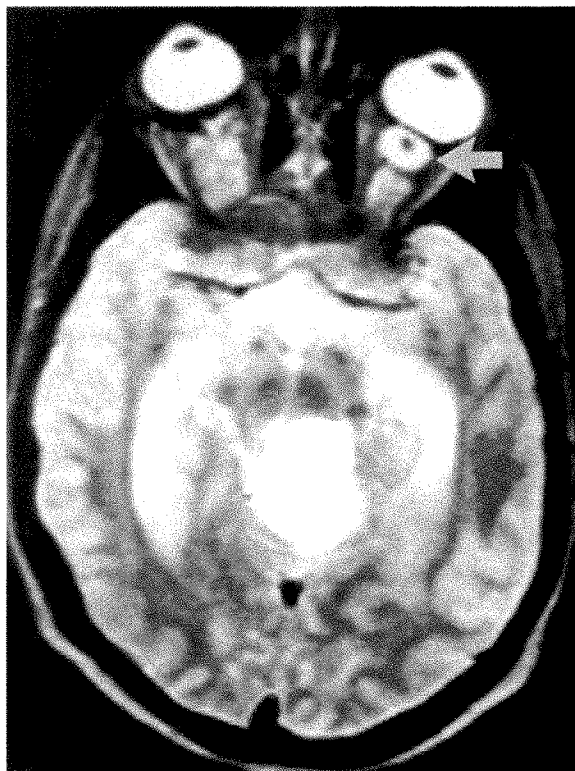


Fig. 3 (Imes and Hoyt). Case 1. Preoperative T_2 -weighted axial magnetic resonance image shows a large mass in the posterior fossa with high signal intensity and dilated lateral ventricles. Anteriorly in the left optic nerve, a thick rim of high signal intensity surrounds a core of lower signal intensity (arrow).



Fig. 4 (Imes and Hoyt). Case 1. Postoperative T₂-weighted axial magnetic resonance image shows resolution of the hydrocephalus. The optic nerve images are unchanged from their preoperative appearance.

small objects with each eye, and her confrontation visual fields were full. Both optic disks were mildly pale.

A T₂-weighted axial image showed tubularly thickened, kinked optic nerves (Fig. 7). Anteriorly, each nerve showed a rim of high signal intensity surrounding a core of low signal intensity.

Case 4

An optic glioma involving the chiasm and both optic nerves was discovered in a 10-month-old boy after his mother noticed fine rotatory movements of his left eye. After a trial of occlusion therapy for amblyopia, the patient was followed up without treatment. When he was 4 years of age, visual acuity was R.E.: central, steady, and maintained and L.E.: central, steady, but not maintained. Left esotropia of 40 prism diopters was observed, and both optic disks were pale. There was no family history of neurofibromatosis, and the child had no signs of neurofibromatosis other than the bilateral optic glioma.

A T₁-weighted parasagittal magnetic resonance image showed tubular thickening of the left orbital optic nerve (Fig. 8). The nerve was elongated and kinked downward in the midorbit. An area of low signal intensity surrounded a core of higher signal intensity. The T₂-weighted axial image showed tubular thickening of both orbital optic nerves (Fig. 9). A zone of high signal intensity surrounded a core of lower signal intensity in both nerves. The left nerve was severely kinked.

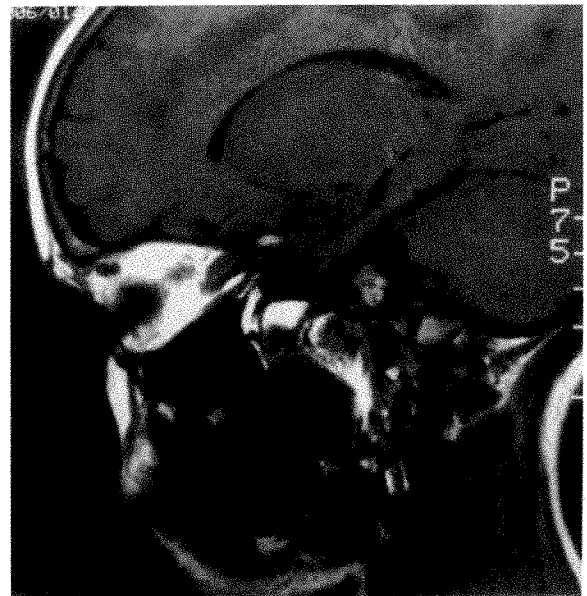
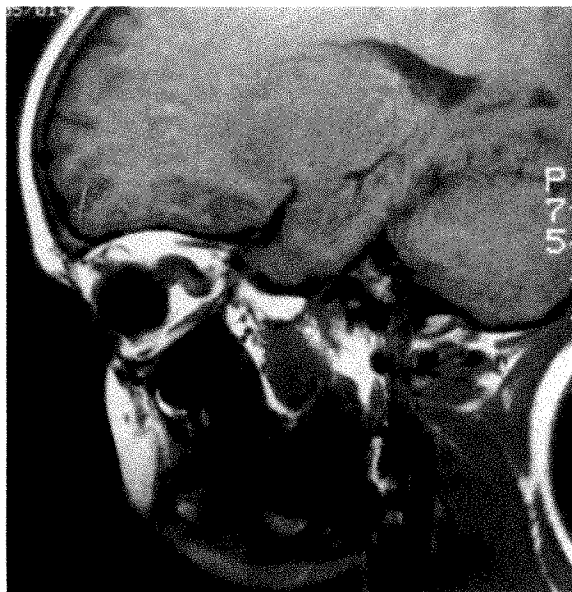


Fig. 5 (Imes and Hoyt). Case 2. T₁-weighted sagittal magnetic resonance images of the left orbit. The optic nerve is tubularly thickened, elongated, and bent sharply downward in the midorbit.

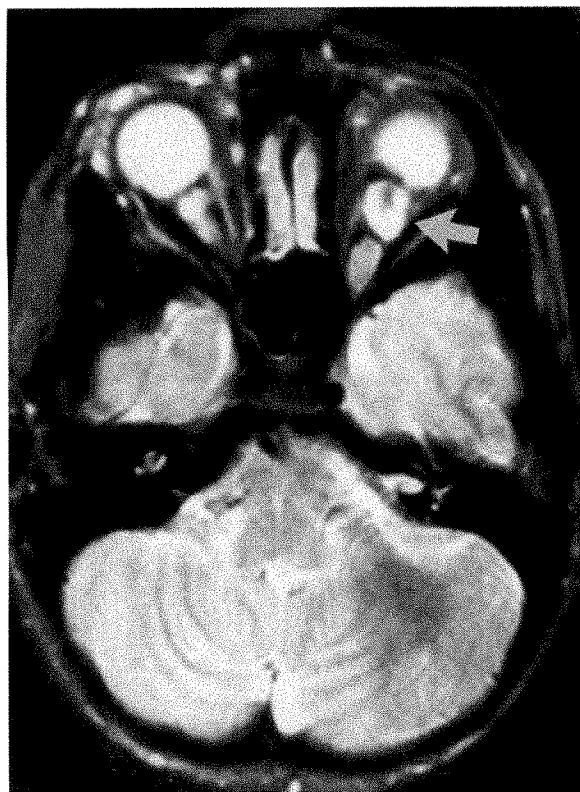


Fig. 6 (Imes and Hoyt). Case 2. T₂-weighted axial magnetic resonance image. Anteriorly in the left optic nerve, an area of high signal intensity surrounds a core of lower signal intensity (arrow).

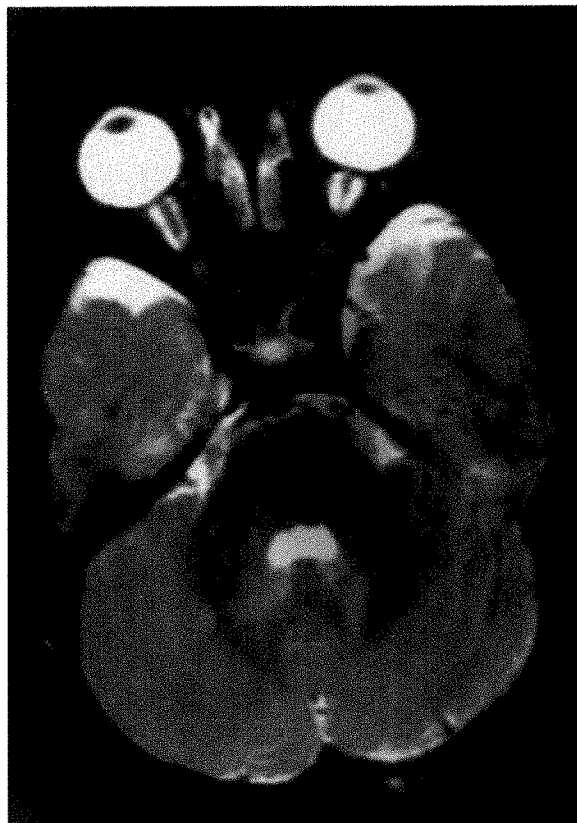


Fig. 7 (Imes and Hoyt). Case 3. T₂-weighted axial magnetic resonance image. The optic nerves are tubularly thickened and kinked. Anteriorly in each nerve, a rim of high signal intensity surrounds a core of low signal intensity.

Discussion

In 1980, Stern, Jakobiec, and Housepian³ reviewed the histopathologic features of 34 orbital optic gliomas. They showed that a circumferential perineural pattern of tumor, which they termed perineural arachnoidal gliomatosis, was highly characteristic of optic nerve gliomas associated with neurofibromatosis 1 (then called von Recklinghausen's neurofibromatosis). Of the 18 tumors from patients with neurofibromatosis 1, 17 had this pattern of tumor growth. From patients without neurofibromatosis 1, however, only two of 16 tumors showed this pattern. In tumors with perineural arachnoidal gliomatosis, the epipial-subarachnoid space was widened by proliferating islands of loosely textured astrocytes or fascicles of astrocytes, intermixed with reactive proliferation of the fibrovascular arachnoidal trabeculae.³ In contrast to the compact neural portion of the

tumor, the perineural subarachnoid component frequently exhibited mucinous and microcystic degeneration in which protoplasmic as well as fibrillary astrocytes were suspended.³

In 1987, Seiff and associates² described a 4-year-old child with neurofibromatosis 1 who had progressive proptosis and blindness of the right eye. T₂-weighted axial magnetic resonance images of the orbital optic nerve showed an area of high signal intensity surrounding a central linear core of lower signal intensity. In histopathologic sections, the tumor had thick myxoid proliferation of glial cells, fibroblasts, meningoepithelial cells, and blood vessels in the subarachnoid space surrounding a more compact intraneural tumor. The authors attributed the perineural rim of high signal intensity in T₂-weighted images to high water content in the myxomatous tissue.

In a 3-year-old boy with neurofibromatosis 1, de Keizer and associates⁴ studied the T₂-

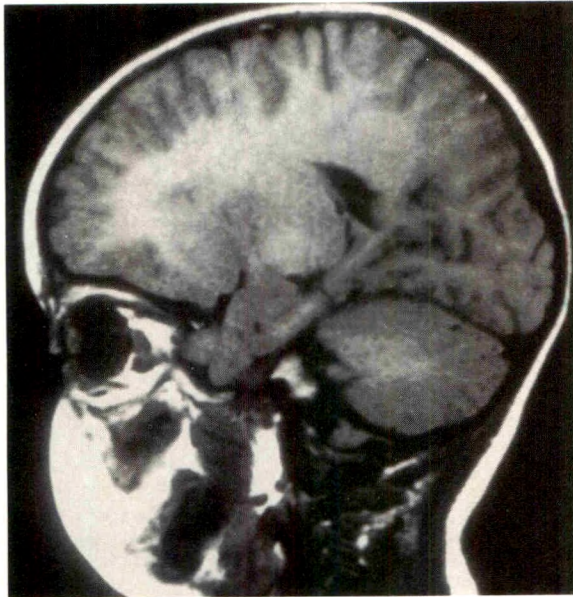


Fig. 8 (Imes and Hoyt). Case 4. T₁-weighted parasagittal magnetic resonance image of the left orbit. The optic nerve is tubularly thickened, elongated, and kinked downward in the midorbit. An area of low signal intensity surrounds a core of higher signal intensity.

weighted axial and sagittal magnetic resonance images, which showed a left optic glioma with high signal intensity surrounding a core of lower signal intensity.⁴ Anteriorly, the nerve buckled downward so sharply that it appeared folded. The high signal intensity corresponded histologically with the description of perineural arachnoidal gliomatosis by Stern, Jakobiec, and Housepian.³

On magnetic resonance images, perineural

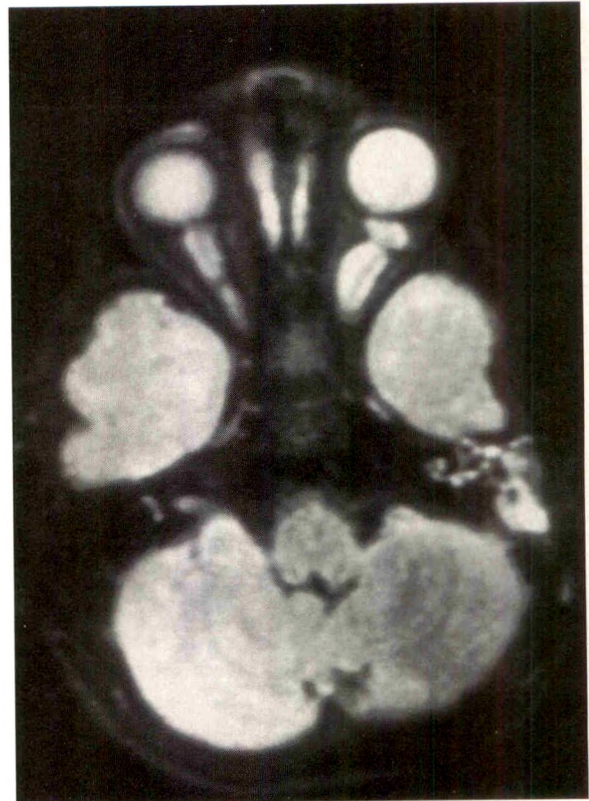


Fig. 9 (Imes and Hoyt). Case 4. T₂-weighted axial magnetic resonance image. A zone of high signal intensity surrounds a core of lower signal intensity in each tubularly thickened optic nerve.

arachnoidal gliomatosis has the signal characteristics of water. Because it surrounds the nerve, it has been mistaken for cerebrospinal

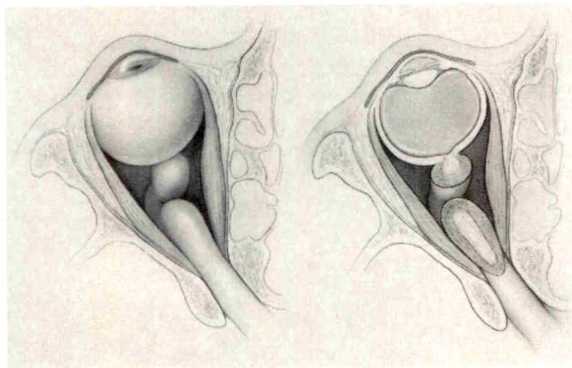


Fig. 10 (Imes and Hoyt). Drawings in axial planes of orbital optic nerve glioma in a patient with neurofibromatosis 1 depicting perineural arachnoidal gliomatosis, tubular thickening, elongation, and downward kinking.

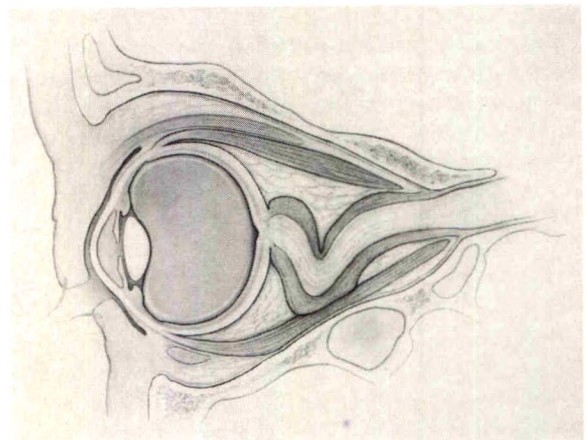


Fig. 11 (Imes and Hoyt). Drawing in a parasagittal plane of orbital optic nerve glioma in a patient with neurofibromatosis 1 depicting perineural arachnoidal gliomatosis, tubular thickening, elongation, and downward kinking.

fluid in a patulous, dilated subarachnoid space.⁵⁻⁸ In Case 1, however, the rim did not diminish in size after relief of hydrocephalus, which proved that the high signal intensity represented tumor, not cerebrospinal fluid.

In all four of our cases, we interpret the waterlike, proton-rich signal surrounding the optic nerves as perineural arachnoidal gliomatosis, an identifying characteristic of orbital glioma in neurofibromatosis 1. Although no café au lait spots were seen in the patient in Case 4, we believe that the orbital tumors of this child were a result of the neurofibromatosis 1 genetic defect.

The magnetic resonance images of our patients showed features of perineural arachnoidal gliomatosis in nerves that were less affected than those previously reported. In one patient (Case 3), imaging was performed on a child with no symptoms as part of a routine examination for neurofibromatosis 1. Another child had one optic nerve that appeared normal ophthalmoscopically and functioned normally, although both optic nerves showed perineural arachnoidal gliomatosis.

Tortuosity of the orbital optic nerve in neurofibromatosis 1, as seen on the sagittal magnetic resonance views in our patients, reflects nerve elongation. This elongation can be striking; in some patients, nerves reach 1½ times their normal length. When elongated, the nerve routinely appears deflected or kinked downward. We speculate that the elongation is caused by axial growth of perineural tumor and that the downward deflection is simply a result of available space in the middle and anterior portions of the orbit. The amount of deflection can be expected to vary with the direction of gaze, and these findings may change with age. The kinking can be extreme in some cases (Figs. 5, left and 8). In the case reported by de Keizer and associates,⁴ the distal optic nerve was buckled on itself.

These findings of double-intensity tubular

thickening, elongation, and downward kinking on magnetic resonance images (Figs. 10 and 11), in addition to bilaterality, indicate the presence of neurofibromatosis 1. Increasingly, these nerve changes will be discovered in prospective surveys of families with neurofibromatosis 1.

References

1. Stern, J., DiGiacinto, G. V., and Housepian, E. M.: Neurofibromatosis and optic glioma. Clinical and morphological correlations. *Neurosurgery* 4:524, 1979.
2. Seiff, S. R., Brodsky, M. C., MacDonald, G., Berg, B. O., Howes, E. L., Jr., and Hoyt, W. F.: Orbital optic glioma in neurofibromatosis. Magnetic resonance diagnosis of perineural arachnoidal gliomatosis. *Arch. Ophthalmol.* 105:1689, 1987.
3. Stern, J., Jakobiec, F. A., and Housepian, E. M.: The architecture of optic nerve gliomas with and without neurofibromatosis. *Arch. Ophthalmol.* 98:505, 1980.
4. de Keizer, R. J. W., de Wolff-Rouendaal, D., Bots, G. T. A. M., Thomeer, R. T. W. M., Brouwer, O. F., and Vielvoye, G. J.: Optic glioma with intraocular tumor and seeding in a child with neurofibromatosis. *Am. J. Ophthalmol.* 108:717, 1989.
5. Holman, R. E., Grimson, B. S., Drayer, B. P., Buckley, E. G., and Brennan, M. W.: Magnetic resonance imaging of optic gliomas. *Am. J. Ophthalmol.* 100:596, 1985.
6. Haik, B. G., Saint Louis, L., Bierly, J., Smith, M. E., Abramson, D. A., Ellsworth, R. M., and Wall, M.: Magnetic resonance imaging in the evaluation of optic nerve gliomas. *Ophthalmology* 94:709, 1987.
7. Bilaniuk, L. T., Zimmerman, R. A., and Newton, T. H.: Magnetic resonance imaging. Orbital pathology. In Newton, T. H., and Bilaniuk, L. T. (eds.): *Modern Neuroradiology*, vol. 4. Radiology of the Eye and Orbit. New York, Raven Press, 1990, p. 5.3.
8. Garrity, J. A., Trautmann, J. C., Bartley, G. B., Forbes, G., Bullock, J. D., Jones, T. W., Jr., and Waller, R. R.: Optic nerve sheath meningoceles. Clinical and radiographic features in 13 cases with a review of the literature. *Ophthalmology* 97:1519, 1990.

The Effect of Preoperative Flurbiprofen on Miosis Produced by Acetylcholine During Cataract Surgery

Jonathan M. Holmes, B.M., B.Ch., and Walter M. Jay, M.D.

Sustained pupillary dilation during cataract surgery may be achieved with preoperative noncorticosteroidal anti-inflammatory agents such as flurbiprofen. However, these agents may interfere with miosis after injection of acetylcholine. Thirty patients for extracapsular cataract extraction were randomly assigned in a double-masked fashion to receive either a placebo or preoperative 0.03% flurbiprofen every 30 minutes for four doses. All patients also received three doses of 2.5% phenylephrine and 2% cyclopentolate. Pupillary diameter was measured the day before surgery, immediately before the surgical incision, immediately before and five minutes after acetylcholine injection, and the morning after surgery. The flurbiprofen group had a larger mean pupillary diameter before injection of acetylcholine ($P < .001$), five minutes after acetylcholine ($P < .001$), and on the first postoperative day ($P < .005$).

PREOPERATIVE NONCORTICOSTEROIDAL anti-inflammatory agents, such as flurbiprofen, have been used in cataract surgery to produce sustained intraoperative pupillary dilation.¹⁻⁶ Premature miosis during cataract surgery may make removing the nucleus, aspirating the cortex, and placing a posterior chamber intraocular lens difficult.^{1,3,4}

At the conclusion of surgery many surgeons inject a cholinergic agent such as acetylcholine to produce pupillary constriction. Inadequate miosis at this stage may increase the incidence of partial or total dislocation of the intraocular lens into the anterior chamber.⁷ The incidence

of partial dislocation has been reported to be 1% to 3%.⁸ These complications may necessitate intraocular lens repositioning, removal, or exchange.

The question of whether the use of preoperative noncorticosteroidal anti-inflammatory drugs interferes with miosis produced by acetylcholine has been investigated in animals.^{7,9} Ozog and associates⁷ demonstrated a reduced miotic response, in albino rabbits, to anterior chamber irrigation with acetylcholine on pretreatment with flurbiprofen. Zimm and associates⁹ found no difference in miosis when experiments were repeated in pigmented rabbits, but their sample size may have been too small for a negative result to be significant.

We investigated the effect of pretreatment with topical flurbiprofen on the miotic effect of acetylcholine during cataract surgery in humans.

Patients and Methods

A randomized, double-masked study of preoperative flurbiprofen and a placebo was performed on pupil size before, during, and after cataract surgery. Thirty-four patients for extracapsular cataract extraction with posterior chamber intraocular lens were enrolled consecutively at a single Veterans Administration Hospital. Patients were enrolled without regard to age, race, or gender. Patients were excluded from enrollment if they had had previous ocular surgery on the affected eye, were taking miotic glaucoma medications, had a history of herpes simplex keratitis, or were taking anticoagulants or anticholinergic medications. Patients were instructed to cease all noncorticosteroidal anti-inflammatory medications for one week before surgery. If they were unable to comply, they were excluded from enrollment. Patients were also excluded from analysis if during the procedure a break in the posterior

Accepted for publication March 26, 1991.

From the Department of Ophthalmology, Loyola University Medical Center, Maywood, Illinois; and Hines Veterans Administration Hospital, Hines, Illinois.

Reprint requests to Jonathan M. Holmes, B.M., B.Ch., Department of Ophthalmology, Loyola University, 2160 S. First Ave., Maywood, IL 60153.

capsule was noted or if sphincterotomies were necessary. Approval from the Human Studies Committee was obtained and informed consent was obtained from each patient meeting the enrollment criteria.

After enrollment patients were randomly assigned to receive either flurbiprofen 0.03% or artificial tears consisting of 1% polyvinyl alcohol (Hypotears). The drops were dispensed in bottles bearing only the patient number and were administered by the ward nursing staff. One drop was given every 30 minutes starting two hours before surgery for a total of four doses (as suggested in the manufacturer's instructions for flurbiprofen). The patients also received 2.5% phenylephrine and 2% cyclopentolate every five minutes for a total of three drops each, starting 30 minutes before surgery.

Surgery was performed by a single surgeon (J.M.H.) who used the same technique. All patients received a Van Lint and retrobulbar anesthetic consisting of 2% lidocaine and 0.75% bupivacaine in a 50/50 mixture with 150 IU of hyaluronidase. The total volume used was 8 ml. Sodium hyaluronate 1% was used before the anterior capsulotomy, and again before insertion of the intraocular lens. The nucleus was expressed by an irrigating lens loop and the cortex was removed with an irrigation/aspiration unit. Sodium hyaluronate was removed before injection of Miochol (1:100 acetylcholine chloride). Epinephrine was used in the irrigating solution (1 ml of 1:10,000 epinephrine in 500 ml of balanced salt solution). A total volume of 1.0 ml of Miochol (1:100 acetylcholine) was injected into the anterior chamber after placement of the intraocular lens and removal of the sodium hyaluronate.

Pupillary diameter was measured to the nearest 0.5 mm, in a manner similar to that described by Stark and associates,³ by a single individual with a millimeter ruler. The greatest pupillary diameter was recorded when the pupil was irregular. Measurements were made on the day before surgery, immediately before the surgical incision, immediately before and five minutes after acetylcholine injection, and the morning after surgery.

Measurements of pupillary diameter were analyzed by analysis of variance with repeated measures and post-hoc tests including Duncan multiple range test, Student-Newman-Keuls test, and contrasts. Chi-square tests and Fisher's exact tests were used to examine the adequacy of randomization.

Results

Of the 34 patients enrolled, four were excluded for the following reasons: failure to receive study drops, operation performed by another surgeon, re-introduction of epinephrine containing balanced salt solution into the eye after injection of acetylcholine, and a tear in the posterior capsule with vitreous loss.

The demographic characteristics of the remaining 30 patients are summarized in Table 1. The distribution of patients within the two treatment groups was similar with regard to age, gender, race, and iris color ($P > .05$). The all-male population resulted from conducting this study at a Veterans Administration Hospital.

The mean pupillary diameters at each stage of surgery are shown in Table 2. Pupillary diameter was greater in the flurbiprofen group immediately before acetylcholine injection ($P < .001$), five minutes after acetylcholine injection ($P < .001$), and on the morning after surgery ($P < .005$). There was no significant difference in the mean pupillary diameter between the two groups, on the day before surgery and immediately before the surgical incision.

The patient excluded for posterior capsule tear and vitreous loss received the placebo. However, the sample size is not sufficient to

TABLE 1
DEMOGRAPHIC CHARACTERISTICS OF PATIENTS

	FLURBIPROFEN GROUP	CONTROL GROUP
No. of patients	17	13
Age (yrs) Mean \pm SD	71 \pm 8	70 \pm 8
Gender		
Male	17	13
Female	0	0
Race		
White	17	11
Nonwhite	0	2
Iris color		
Blue	8	4
Brown	4	6
Hazel	5	1
Green	0	2
Eye		
R.E.	12	4
L.E.	5	9

TABLE 2
MEAN PUPIL DIAMETERS

	FLURBIPROFEN GROUP (mm) \pm SD	CONTROL GROUP (mm) \pm SD	SIGNIFICANCE OF DIFFERENCE BETWEEN GROUPS
Day before surgery	3.0 \pm 0.7	3.1 \pm 0.5	NS*
Immediately before surgical incision	8.1 \pm 0.7	7.8 \pm 0.7	NS*
Immediately before acetylcholine injection	7.6 \pm 0.7	6.2 \pm 0.9	P < .001
Five minutes after acetylcholine injection	4.9 \pm 0.7	3.8 \pm 0.6	P < .001
Morning after surgery	4.4 \pm 1.1	3.6 \pm 0.7	P < .005

*Not significant.

draw conclusions from this finding. Other than this possible adverse effect, no side effects or adverse reactions were noted from instillation of either flurbiprofen or the placebo.

Discussion

The role of noncorticosteroidal anti-inflammatory drugs in sustaining mydriasis during cataract surgery has already been established.¹⁻⁶ Double-masked studies have been performed using indomethacin,² flurbiprofen,⁴ and suprofen,³ which show reduced miosis when compared to eyes pretreated with a placebo. Our results support the findings of these previous studies; the mean pupillary diameter was greater before injection of acetylcholine in the flurbiprofen group when compared to the control group. It has been suggested that these agents act by inhibition of the cyclo-oxygenase-mediated release of prostaglandins.³ Prostaglandins have been implicated in pupillary constriction secondary to ocular trauma.¹ Bito¹⁰ disagreed with this proposed mechanism, suggesting that there is little direct evidence of prostaglandins mediated constriction of the human iris sphincter. He further suggested that cyclo-oxygenase inhibitors may act by inhibiting the synthesis of prostaglandins, which would potentiate the substance-P induced miotic response to trauma.

In the previous human studies on pretreatment with noncorticosteroidal anti-inflammatory drugs²⁻⁴ the final pupillary diameter was

measured either before or without the injection of acetylcholine. The use of a miotic such as acetylcholine has been common for several decades.¹¹ There have been reports (manufacturer's package insert) of a reduced miotic response to acetylcholine in patients treated with flurbiprofen. Such an interaction has been investigated in rabbits. Ozog and associates⁷ demonstrated a reduced miotic response to acetylcholine to anterior chamber irrigation with acetylcholine in albino rabbits. Zimm and associates⁹ found no difference in miosis to acetylcholine when the experiment was repeated in pigmented rabbits, but their sample size was too small for a negative result to be conclusive. Our study was specifically designed to evaluate the interaction of pretreatment with flurbiprofen on miosis produced by acetylcholine in humans.

We found that the mean pupillary diameter in the flurbiprofen group was significantly greater than in the control group at five minutes after injection of acetylcholine and on the first post-operative day. This difference in pupillary diameter between the flurbiprofen and control group five minutes after acetylcholine injection may be a reflection of the difference before injection. Acetylcholine is a direct agonist acting at the level of the motor end plates. There seems to be no theoretical basis for an inhibition of acetylcholine by a noncorticosteroidal anti-inflammatory agent. Indeed, when we examined the change in pupillary diameters from pre- to postacetylcholine injection, there was no difference between the flurbiprofen group (2.6 \pm 0.7 mm) and the control group (2.3 \pm 0.9 mm, P = .4). This finding contradicts that of Ozog and associates⁷ but there are clear differences between the two studies. In our study cataract surgery was performed with resultant trauma to the iris. Whether miosis induced by trauma is mediated by prostaglandins, substance-P, or some yet to be defined factor, flurbiprofen acts in the early part of surgery to reduce trauma-induced miosis. Therefore, the pupillary diameters before acetylcholine must be different in the flurbiprofen and control groups. In the albino rabbit experiment of Ozog and associates,⁷ no surgery was performed and the baseline pupillary diameters were equal. Therefore, their animal model does not represent the clinical situation.

Acetylcholine is known to be a miotic of short duration. Rizzuti¹² noted its duration to be 20 minutes or less, Elliott and Carter¹³ demonstrated no miotic effect after six hours. Therefore,

the pupillary diameter measured on the morning after surgery may not be influenced by acetylcholine injected during surgery. The difference between the flurbiprofen and control groups could then be explained on the basis of administration of flurbiprofen alone. Our finding of a larger pupillary diameter in the flurbiprofen group on the morning after surgery would suggest that the effect of flurbiprofen in maintaining pupillary dilation may last until at least the morning after surgery.

We have shown that flurbiprofen administered preoperatively results in a larger pupillary diameter after removal of the lens and placement of intraocular lens after injection of acetylcholine and on the first postoperative day. Flurbiprofen does not appear to inhibit the effect of acetylcholine. Flurbiprofen does reduce trauma-induced miosis, and therefore subsequent pupillary diameters are larger. Whether this is clinically significant is unclear. The incidence of partial, anterior dislocation of the intraocular lens has been estimated to be 1% to 3%.⁸ In order to detect a significant difference in partial dislocation rate a large randomized trial would need to be conducted.

References

1. Duffin, R. M., Camras, C. B., Gardner, S. K., and Pettit, T. M.: Inhibitors of surgically induced miosis. *Ophthalmology* 89:966, 1982.
2. Keulen-De Vos, H. C. J., Van Rij, G., Renardel de Lavalette, J. C. G., and Jansen, J. T. G.: Effect of indomethacin in preventing surgically induced miosis. *Br. J. Ophthalmol.* 67:94, 1983.
3. Stark, W. J., Fagadau, W. R., Stewart, R. H., Crandall, A. S., de Faller, J. M., Reaves, T. A., and Klein, P. E.: Reduction of pupillary constriction during cataract surgery using suprofen. *Arch. Ophthalmol.* 104:364, 1986.
4. Keates, R. H., and McGowan, K. A.: Clinical trial of flurbiprofen to maintain pupillary dilation during cataract surgery. *Ann. Ophthalmol.* 16:919, 1984.
5. Keates, R. H., and McGowan, K. A.: The effect of topical indomethacin ophthalmic solution in maintaining mydriasis during cataract surgery. *Ann. Ophthalmol.* 16:1116, 1984.
6. Drews, R. C., and Katsev, D. A.: Ocufen and pupillary dilation during cataract surgery. *J. Cataract Refract. Surg.* 15:445, 1989.
7. Ozog, M. F., Zimm, J. L., Park, R., Fisher, S., Fort, C., and McDonald, J. E.: Evaluation of flurbiprofen exposed irises to acetylcholine anterior chamber irrigation. *J. Cataract Refract. Surg.* 16:226, 1990.
8. Goodman, D. F., Stark, W. J., and Gottsch, J. D.: Complications of cataract extraction with intraoperative lens implantation. *Ophthalmic Surg.* 20:132, 1989.
9. Zimm, J. L., Holmes, J. M., Anderson, C., and Evans, L. S.: Effects of topical anti-prostaglandins on miosis produced by anterior chamber irrigation with cholinergic agonists. ARVO abstracts. Supplement to Invest. Ophthalmol. Vis. Sci. Philadelphia, J. B. Lippincott, 1990, p. 508.
10. Bito, L. Z.: Surgical miosis. Have we been misled by a bunch of rabbits? *Ophthalmology* 97:1, 1990.
11. Douglas, G. R.: A comparison of acetylcholine and carbachol following cataract extraction. *Can. J. Ophthalmol.* 8:75, 1973.
12. Rizzuti, A. B.: Acetylcholine in surgery of the lens iris and cornea. *Am. J. Ophthalmol.* 63:484, 1967.
13. Elliott, A., and Carter, C.: Pupil size after extracapsular cataract extraction and posterior chamber lens implantation. A prospective randomized trial of epinephrine and acetylcholine. *Ophthalmic Surg.* 20:591, 1989.

OPHTHALMIC MINIATURE

He had gotten considerably fatter, and a Syrian goldsmith had made him a new eye of gold and precious stones, of which he was exceedingly proud although it chafed the socket so badly that he took it out as soon as he had sat down beside me under the sycamore.

Mika Waltari, *The Egyptian*
Helsinki, WSOY, 1983, p. 489-490

The Effect of Allograft Rejection After Penetrating Keratoplasty on Central Endothelial Cell Density

David C. Musch, Ph.D., Ann E. Schwartz, M.D., Karen Fitzgerald-Shelton, B.S., Alan Sugar, M.D., and Roger F. Meyer, M.D.

We identified all patients who had undergone penetrating keratoplasty for keratoconus and were being observed longitudinally (N = 174). During the follow-up period, 57 of 174 patients (33%) showed evidence of an allograft rejection episode, which occurred at an average of eight months after the operation. We analyzed specular photographs of the corneal endothelium, taken before and after the first allograft rejection episode. A significant decrease in endothelial cell density was observed (11.8%, $P < .0001$). As a control, we analyzed all available specular photographs from patients with keratoconus who showed no evidence of allograft rejection after penetrating keratoplasty. The observed endothelial cell density decrease (11.8%) in patients with keratoconus undergoing allograft rejection exceeded that found in the control subjects (6.8%) during a comparable time period ($P = .06$). Severe allograft rejection episodes resulted in a decrease in endothelial cell density that exceeded expected loss significantly (14.8% compared with 6.9%, $P = .01$), whereas mild allograft rejection episodes were not associated with a loss in endothelial cell density exceeding that expected (1.8% compared with 6.5%, $P = .34$).

AMONG THE PREVALENT CAUSES of graft failure after penetrating keratoplasty, immunologic rejection of the grafted tissue, termed allograft rejection, is a leading etiologic factor.¹ It has been estimated that 30% of corneal grafts un-

dergo at least one allograft rejection,^{2,4} and one third or more of these grafts fail after unsuccessful treatment with corticosteroids or other immunosuppressive therapy. Although the clinical appearance of the rejection episode can vary from a well-demarcated line of keratic precipitates advancing across the graft endothelium to a diffuse scattering of keratic precipitates,^{5,6} prompt recognition and treatment of an allograft rejection is critical to preserving the clarity of the graft.

The allograft rejection results from recognition of the grafted tissue by the immune system, and the response is characterized by destruction of the graft's endothelial cells by cell-mediated, cytotoxic lymphocytes.⁷ We attempted to quantify the impact of allograft rejection on endothelial cell density, an often-used morphologic indicator for the graft's functional integrity. Also, we attempted to determine the relationship between allograft rejection severity and loss of endothelial cell density.

Patients and Methods

Since we desired to identify a group of patients who had undergone penetrating keratoplasty, who are known to have a high risk of allograft rejection, and usually lack other factors that can affect endothelial cell density, such as the presence of an intraocular lens, we selected patients undergoing penetrating keratoplasty for keratoconus as the study subjects. Using the computerized information on patients undergoing penetrating keratoplasty contained in the Michigan Corneal Transplantation Registry, which is complete for all penetrating keratoplasty procedures conducted at the Kellogg Eye Center from 1980 through 1985, we identified 206 penetrating keratoplasty procedures performed for keratoconus in 174 patients. We accessed the medical records of these 174 patients to identify those who under-

Accepted for publication March 8, 1991.

From the Department of Ophthalmology, Kellogg Eye Center, University of Michigan, Ann Arbor, Michigan. This study was supported in part by an unrestricted, departmental grant from Research to Prevent Blindness, Inc.

Inquiries to David C. Musch, Ph.D., Kellogg Eye Center, University of Michigan, 1000 Wall St., Ann Arbor, MI 48105-1994.

went an allograft rejection episode during the follow-up period after their first penetrating keratoplasty. Diagnosis of an allograft rejection was made when a graft that was clear for at least two weeks after penetrating keratoplasty had onset of an inflammatory reaction in the anterior chamber, with the presence of keratic precipitates on the graft's endothelium in association with stromal edema. The severity of the allograft rejection episode was termed mild if there were one to five keratic precipitates present and less than a 10% increase in corneal thickness, relative to the last visit, at the time the allograft rejection was diagnosed. If there were more than five keratic precipitates present or an increase of 10% or greater in corneal thickness at the time the allograft rejection was diagnosed, relative to the last visit, the allograft rejection was classified as severe.⁸

During routine clinical follow-up of all patients after penetrating keratoplasty, a specular photograph was obtained at two weeks, three, six, 12, and 18 months, and annually thereafter, using a contact specular microscope. Upon identifying patients with evidence of an allograft rejection, we then selected the specular photographs that were taken within the shortest available time preceding the onset of the allograft rejection and following the resolution of the allograft rejection and counted three central visual fields by fixed-frame analysis.⁹ The average of these counts was used to represent the patient's central endothelial cell density at each time point. As a control group, we obtained and counted all available specular photographs obtained during follow-up of patients with keratoconus who showed no signs of allograft rejection during the follow-up period after penetrating keratoplasty. These counts were used to generate the expected loss of endothelial cell density over time intervals comparable to those in the patients with keratoconus who underwent allograft rejection. Statistical comparisons were made by the independent or paired, two-tailed Student's *t*-test.

Results

During the follow-up period after the initial penetrating keratoplasty in 174 patients who required penetrating keratoplasty for keratoconus, 57 (33%) showed evidence of at least one allograft rejection episode, of which the first

occurred at a median time of eight months after penetrating keratoplasty. Specular photographs were available for times preceding and following the allograft rejection episode for 53 (93%) of these 57 patients. All of the 57 patients with keratoconus who had an allograft rejection episode were treated successfully; therefore, the four patients who lacked specular photographs either before or after their allograft rejection episode were not photographed because of scheduling rather than graft-status reasons. When the timing of the specular photographs was inspected, data on five patients were excluded, because of our inability to provide an expected endothelial cell density loss value from the control information. For example, one patient underwent the first allograft rejection episode 97 months after penetrating keratoplasty, and specular photographs were available at 84 and 108 months after penetrating keratoplasty. Our control information could not provide a reliable estimate of the expected endothelial cell density loss for this interval, and so the data on this patient were excluded from further analysis. Therefore, observed and expected endothelial cell density loss information was available for 48 patients.

Expected endothelial cell density loss in the absence of an allograft rejection was generated from all available specular photographs from the follow-up of patients with keratoconus after penetrating keratoplasty who did not undergo allograft rejection ($N = 117$); the expected values (median percent loss of endothelial cell density) are based upon a variable sample size (Table). Expected endothelial cell density loss information was available from more than 20 patients for all of the possible follow-up intervals during the first three years after penetrating keratoplasty.

Observed percent loss of endothelial cell density from before to after the allograft rejection episode was 11.8% (standard deviation, 17.9%), which was significantly greater than a null hypothesis of no loss (95% confidence interval, 6.6% to 17.0%, $P < .0001$). When the patients were divided into those with severe and mild allograft rejection, a significantly greater average percent loss of endothelial cell density ($P = .03$) was observed in those with severe allograft rejection episodes, 14.8% (standard deviation, 17.9%), compared with that observed in patients with a mild allograft rejection episode, 1.8% (standard deviation, 14.5%). Furthermore, the observed percent loss of endothelial cell density was statistically sig-

TABLE
EXPECTED PERCENT LOSS OF CORNEAL
ENDOTHELIAL CELL DENSITY AFTER PENETRATING
KERATOPLASTY IN THE ABSENCE OF ALLOGRAFT
REJECTION*

FOLLOW-UP INTERVAL (mos)	NO. OF PAIRED COUNTS AVAILABLE†	MEDIAN PERCENT LOSS OF ENDOTHELIAL CELL DENSITY
0.5-3.0	47	2.5
0.5-6.0	48	6.3
0.5-12.0	40	12.0
0.5-24.0	30	12.5
0.5-36.0	23	18.2
3.0-6.0	72	4.0
3.0-12.0	65	6.0
3.0-24.0	40	11.8
3.0-36.0	28	23.9
6.0-12.0	63	6.8
6.0-24.0	40	9.6
6.0-36.0	27	21.7
12.0-24.0	36	2.4
12.0-36.0	26	17.2
24.0-36.0	23	13.2

*Obtained from patients undergoing penetrating keratoplasty for keratoconus.

†A paired count is defined as an endothelial cell density estimate available for an individual patient at both timepoints.

nificant in patients with severe allograft rejection (95% confidence interval, 8.8% to 20.8%, $P < .0001$), whereas the loss in those with mild allograft rejection was insignificant ($P = .68$).

Upon comparing the observed percent loss of endothelial cell density with that expected during a comparable time interval, the observed percent loss of endothelial cell density (for all patients) was not significantly greater than that expected (11.8% compared with 6.8%, $P = .06$), although the direction of the difference was consistent with a detrimental effect of allograft rejection. When severe allograft rejection episodes were evaluated separately, however, the observed percent loss of endothelial cell density (14.8%) was significantly greater than that expected (6.9%; $P = .01$). The percent loss of endothelial cell density observed in mild allograft rejection episodes (1.8%) did not significantly differ from that expected (6.5%; $P = .34$).

Discussion

Immunologic recognition of transplanted tissue is a potential complication shared by all recipients of donor organs and tissue. In corneal transplantation, the focus of the immune-mediated attack on the grafted tissue is the corneal endothelial cells. These cells are vital to maintenance of the clarity of the graft, since they provide the mechanism, by barrier and active transport processes, for preventing the corneal stroma from swelling to an edematous state. Given the importance of these cells, their destruction during an allograft rejection episode can lead to failure of the graft, which necessitates regrafting. Although the relationship between endothelial cell density and graft clarity is not direct, there is evidence of a diminishing capacity to maintain clarity with a low endothelial cell density.¹⁰

In one study that assessed long-term changes in endothelial cell density after penetrating keratoplasty, a 21% decrease in endothelial cell density per year for three years was observed, after which the endothelial cell density was stable.¹¹ In the studies that have addressed the effect of allograft rejection on endothelial cell density, qualitative morphologic changes to the endothelium have been described,^{12,13} and low endothelial cell density values after allograft rejection have been reported.^{14,15} Bourne, McCarey, and Kaufman¹⁶ reported significant loss of endothelial cell density in a patient undergoing allograft rejection, and Ruusuvaara¹⁷ reported that the endothelial cell density of eight patients undergoing allograft rejection was 20% less than the remaining 94 patients who had no rejection over a variable follow-up interval. In 26 grafts examined before and after allograft rejection, Bourne¹¹ observed a 28% mean cell loss. In all of these studies, however, control for the expected loss of endothelial cell density during the follow-up window from before to after allograft rejection was lacking, as was information on the impact of allograft rejection severity on endothelial cell density loss.

We made an effort to control for the expected decrease in endothelial cell density seen after penetrating keratoplasty by quantifying the observed loss over multiple time intervals in patients who were similar to those who underwent an allograft rejection episode in every respect other than the experience of an allograft

rejection episode. When severe and mild allograft rejection episodes were combined, the observed loss of endothelial cell density (11.8%) was larger than that expected (6.8%), and the difference was of borderline statistical significance ($P = .06$). This result, however, was influenced greatly by the severity of the allograft rejection episode. Episodes in which there were greater than five keratic precipitates, more than a 10% increase in corneal thickness associated with the allograft rejection, or both were termed severe, and the observed loss of endothelial cell density associated with these episodes was significantly greater than expected endothelial cell density loss. Mild episodes showed no significant loss of endothelial cell density.

These findings provide support to the importance of early detection of an allograft rejection episode. Although most of our patients had severe allograft rejection episodes, those that were detected early in the course of the allograft rejection, as evidenced by one to five keratic precipitates and less than a 10% increase in corneal thickness from the previous visit, lost no more endothelial cells than that expected in the absence of an allograft rejection. Severe episodes, however, showed a concomitant decrease in endothelial cell density that exceeded expected loss significantly.

It is reasonable to assume that most allograft rejection episodes in an avascular graft are initially mild and become more severe over time. A time window exists, therefore, in which a detected allograft rejection can be treated and endothelial cell loss prevented. It is imperative, therefore, that patients are instructed and continually reminded of the signs and symptoms of allograft rejection, so that early detection and effective treatment can be instituted.

References

1. Khodadoust, A. A.: The allograft rejection reaction. The leading cause of late failure of clinical corneal grafts. In Porter, R., and Knight, J. (eds.): *Corneal Graft Failure*, Ciba Foundation Symposium 15 (new series). Amsterdam, Associated Scientific Publishers, 1973, pp. 151-163.
2. Chandler, J. W., and Kaufman, H. E.: Graft reactions after keratoplasty for keratoconus. *Am. J. Ophthalmol.* 77:543, 1976.
3. Aldredge, O. C., and Krachmer, J. H.: Clinical types of corneal transplant rejection. Their manifestations, frequency, preoperative correlates and treatment. *Arch. Ophthalmol.* 99:599, 1981.
4. Musch, D. C., and Meyer, R. F.: Risk of endothelial rejection following bilateral penetrating keratoplasty. *Ophthalmology* 96:1139, 1989.
5. Kok-van Alphen, C. C., Volker-Dieben, H. J. M., van der Want, J. J. L., and Vrensen, G.: Rejected human corneal grafts. I. Clinical study. *Doc. Ophthalmol.* 50:275, 1981.
6. Polack, F. M.: Clinical and pathological aspects of the corneal graft reaction. *Trans. Am. Acad. Ophthalmol. Otolaryngol.* 77:418, 1973.
7. Grunnet, N., Kristensen, T., Kissmeyer-Nielsen, F., and Ehlers, N.: Occurrence of lymphocytotoxic lymphocytes and antibodies after corneal transplantation. *Acta Ophthalmol.* 54:167, 1986.
8. Collaborative Corneal Transplantation Studies: Manual of Operations. Springfield, Virginia, National Technical Information Service, Accession No. PB90-1349251AS, April 1988, Chap. 9, Sec. 9.93, p. 9-8.
9. Bourne, W. M., and Kaufman, H. E.: Specular microscopy of human corneal endothelium in vivo. *Am. J. Ophthalmol.* 81:319, 1976.
10. Hoffer, K. J.: Corneal decompensation after corneal endothelium cell count. *Am. J. Ophthalmol.* 87:252, 1979.
11. Bourne, W. M.: Morphologic and functional evaluation of the endothelium of transplanted human corneas. *Trans. Am. Ophthalmol. Soc.* 81:403, 1983.
12. Olsen, T.: The specular microscopic appearance of corneal graft endothelium during an acute rejection episode. A case report. *Acta Ophthalmol.* 57:882, 1979.
13. Hirst, L. W., and Stark, W. J.: Clinical specular microscopy of corneal endothelial rejection. *Arch. Ophthalmol.* 101:1387, 1983.
14. Bourne, W. M., Doughman, D. J., and Lindstrom, R. L.: Organ-cultured corneal endothelium in vivo. *Arch. Ophthalmol.* 95:1818, 1977.
15. Linn, J. G., Jr., Stuart, J. C., Warnicki, J. W., Sinclair, R. A., and Marsh, G. M.: Endothelial morphology in long-term keratoconus corneal transplants. *Ophthalmology* 88:761, 1981.
16. Bourne, W. M., McCarey, B. E., and Kaufman, H. E.: Clinical specular microscopy. *Trans. Am. Acad. Ophthalmol. Otolaryngol.* 81:743, 1976.
17. Ruusuvaara, P.: Histocompatibility and corneal graft endothelium. *Acta Ophthalmol.* 57:968, 1979.

Comparison of Intraocular Lens Fixation Techniques Performed During Penetrating Keratoplasty

Richard M. Davis, M.D., Douglas Best, M.D., and Gregory E. Gilbert, B.A.

We reviewed the charts of 41 patients who had undergone penetrating keratoplasty, anterior vitrectomy, and placement or exchange of an intraocular lens during a two-year period with a median follow-up time of 15 months (range, five to 26 months). The median preoperative visual acuity was 20/400 (range, 20/40 to hand motions). The median postoperative visual acuity was 20/70 (range, 20/25 to hand motions). Of 41 corneal grafts, 38 (93%) remained clear. New intraocular lenses were inserted by anterior chamber, iris, or transscleral fixation. The median visual acuity was 20/70 for the anterior chamber lens group, 20/100 for the iris fixation group, and 20/70 for the transscleral fixation group. Analysis of variance demonstrated no significant difference by type of fixation in postoperative visual acuity, central corneal thickness, and intraocular pressure.

THE USUAL SURGICAL MANAGEMENT of pseudophakic corneal edema is a penetrating keratoplasty with removal of an iris-supported or a closed-loop anterior chamber intraocular lens. There is no consensus concerning the type of intraocular lens implanted as part of the exchange procedure.¹ The main advantage of an anterior chamber intraocular lens is the ease of implantation and decreased operating time. Late graft failure, progressive endothelial cell loss, peripheral anterior synechiae, and secondary glaucoma have caused some ophthalmologists to prefer sutured posterior chamber lenses. Although several studies evaluated single fixation techniques, direct comparison is diffi-

cult because testing is not standardized. Few studies have contrasted anterior chamber and iris-sutured posterior chamber lenses.^{2,3} We compared the results of 41 patients who had undergone anterior chamber, transscleral, or iris fixation of an intraocular lens at the time of penetrating keratoplasty for the treatment of pseudophakic corneal edema.

Patients and Methods

We reviewed the charts of 41 consecutive patients who had undergone penetrating keratoplasty, intraocular lens exchange, and anterior vitrectomy between September 1987 and September 1989. Pseudophakic or aphakic corneal edema was diagnosed in all patients. Results recorded from the last examination included the manifest refraction, best-corrected visual acuity, intraocular pressure by pneumotonometer, ultrasonic pachymetry, slit-lamp biomicroscopy, and ophthalmoscopy. All surgical procedures were performed by one of us (R.M.D.).

General endotracheal or local anesthesia was administered. Local anesthesia included an O'Brien facial nerve block and a retrobulbar injection of a 1:1 mixture of 2% lidocaine and 0.75% bupivacaine hydrochloride with 150 USP units of hyaluronidase. Preoperative mydriasis was accomplished with cyclopentolate hydrochloride 1% and phenylephrine hydrochloride 2.5% and was stabilized with flurbiprofen sodium 0.03%. A Flieringa ring was sutured to the sclera with 8-0 silk to prevent scleral collapse after removal of the recipient cornea. The donor cornea was removed from its storage medium and cut endothelial side up on a Teflon block with a 7.5- or 8.0-mm cutting trephine. The donor cornea was sized 0.5 mm larger than the diameter of the recipient trephination. The area of the cornea corresponding to the visual axis was indented with a Sinsky hook. A 5.0-mm blunt trephine was then cen-

Accepted for publication March 14, 1991.

From the Department of Ophthalmology, University of South Carolina School of Medicine, Columbia, South Carolina.

Reprint requests to Richard M. Davis, M.D., Department of Ophthalmology, 4 Richland Medical Park, Columbia, SC 29203.

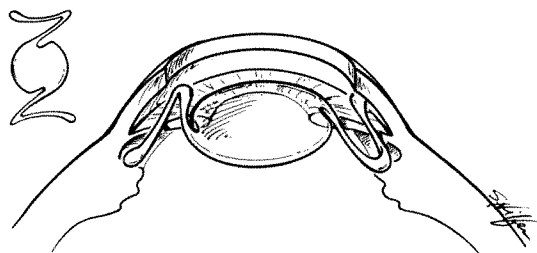


Fig. 1 (Davis, Best, and Gilbert). An anterior chamber lens with four-point fixation was used for anterior chamber angle fixation.

tered around the visual axis indentation to obtain a circular reference mark that assisted in centering the recipient trephine. The recipient cornea was incised with a Hessburg-Barron vacuum suction trephine to the approximate level of Descemet's membrane. The anterior chamber was entered with a sharp disposable knife. Corneal scissors were used to remove the recipient cornea and to preserve carefully a posterior corneal lip. If present, the intraocular lens was removed carefully. An open-sky automated anterior vitrectomy was performed with a suction of 200 mm Hg and 500 cuts per minute cutting rate to remove vitreous from the anterior chamber angle, iris, and anterior ciliary body. A cell sponge placed gently on the anterior iris surface was used to detect residual vitreous. Goniosynechiolysis was performed in selected cases. Anterior chamber angle hemostasis was controlled with sodium hyaluronate.

The intraocular lens used depended on the fixation technique. A one-piece four-point fixation anterior chamber lens was used for anterior chamber angle fixation in ten eyes (Fig. 1). The orientation of the anterior chamber lens inserted matched the orientation of the explanted anterior chamber lens. The haptics were adjusted with a Sinsky hook to avoid iris distortion. A three-piece biconvex posterior chamber lens with four optic positioning holes was used for iris fixation in eight eyes (Fig. 2). A needle from a 10-0 polypropylene suture was passed through the midperipheral iris, down through an optic positioning hole, and up through the adjacent optic positioning hole. The needle was then directed through the posterior iris surface to the anterior chamber and tied to the free end of the suture. The knot was placed on the midperipheral anterior iris surface. A one-piece posterior chamber lens of 12.8 mm in overall length was used for transscleral fixation in 23 eyes (Fig. 3). A 10-0 polypropylene suture was

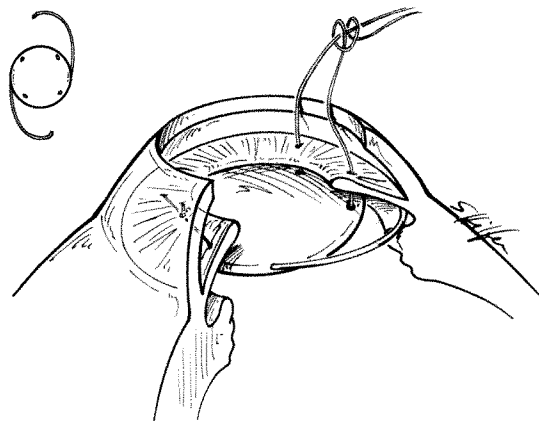


Fig. 2 (Davis, Best, and Gilbert). Iris fixation of a posterior chamber lens was achieved by placing two 10-0 polypropylene sutures, one suture each, through two optic holes, and tied to the anterior midperipheral iris.

cut in half and each end was tied to a loop of the posterior chamber lens. Each knot was placed at a point on the loop farthest from the optic. The distance from the end of the loop to the knot was then approximately equal for both knots. Each needle was then directed under the iris at the 2 o'clock and 8 o'clock meridians to exit the sclera 1.0 mm posterior to the corneoscleral limbus. The polypropylene suture was then tied to itself under a lamellar scleral flap or one end was buried in the sclera, which left an exposed loop of suture under the conjunctiva.

The first eight consecutive posterior chamber lenses were inserted by the iris fixation technique; the subsequent 23 posterior chamber intraocular lenses were implanted by the scleral fixation technique. The surgical technique

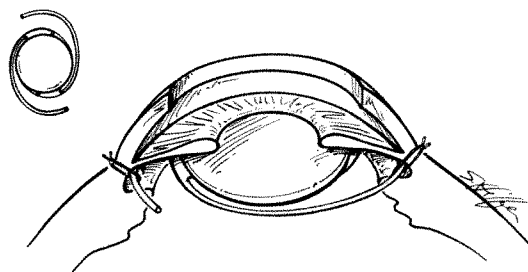


Fig. 3 (Davis, Best, and Gilbert). A one-piece posterior chamber lens of 12.8 mm in length was sutured transsclerally by tying a 10-0 polypropylene suture to each haptic and directing the needle under the iris and through the sclera 1 mm posterior to the corneoscleral limbus.

evolved to transscleral fixation because of possible loop instability with the iris fixation technique. Anterior chamber lenses were inserted at the request of a referring ophthalmologist. No other factors were considered in selecting an intraocular lens fixation technique. Therefore, 41 patients who had undergone intraocular lens fixation by one of three fixation techniques were available for analysis.

Power of the intraocular lens was derived from the modified Sanders-Retzlaff-Kraff formula with an average keratometry reading of 43.50 diopters based on previous keratoplasty procedures (R.M.D.). After placement of the intraocular lens, sodium hyaluronate was injected into the anterior chamber and on the recipient corneal rim. The donor cornea was sutured with eight interrupted 10-0 nylon sutures. The sodium hyaluronate was then exchanged for balanced salt solution. Eight additional 10-0 nylon interrupted sutures were placed if the recipient cornea had greater than 30 degrees of vascularization; otherwise a 16-bite antitorque 10-0 nylon suture was placed. All interrupted suture knots were buried under the recipient corneal epithelium. After intraocular pressure returned to normal with balanced salt solution, qualitative keratotomy was performed with a handheld cylindric keratoscope. Suture adjustment was performed until a circular light reflex was obtained. Subconjunctival injections of 40 mg of gentamicin sulfate, 125 mg of cefazolin, and 4 mg of dexamethasone were administered, and an antibiotic-corticosteroid ointment was placed on the eye after removal of the Flieringa ring. A pressure patch was applied.

Results

Five of 41 eyes underwent secondary intraocular lens insertion for aphakic bullous keratopathy, and the remaining 36 eyes underwent intraocular lens exchange for pseudophakic corneal edema (Table). The mean age of the patients at the time of keratoplasty was 75.7 years (range, 42 to 88 years). Eleven patients were men, and 30 patients were women. Surgery was performed on 27 right eyes and 14 left eyes. The average interval from cataract extraction to the onset of corneal edema was approximately 74 months (range, zero to 238 months). The average interval from onset of corneal edema after cataract extraction to the date of kera-

toplasty was approximately 15 months (range, two to 64 months). An anterior chamber lens was inserted into ten eyes, an iris-sutured posterior chamber lens in eight eyes, and a ciliary-sulcus-fixated posterior chamber lens in 23 eyes.

An intraocular lens was explanted in 36 of 41 eyes: 34 were closed-loop anterior chamber lenses, one was an iris-clip intraocular lens, and one was a posterior chamber intraocular lens. Thirty-eight of 41 (93%) corneal grafts remained clear. Two eyes had immunologic graft failure, and one graft had surface irregularities secondary to ocular surface disease.

The mean preoperative and postoperative intraocular pressures for all eyes were 14.9 ± 0.68 mm Hg (range, 6.4 to 28.0 mm Hg) and 16.6 ± 0.78 mm Hg (range, 8.9 to 31.1 mm Hg), respectively, which was not statistically significant (paired *t*-test, $P = .102$). The mean intraocular pressure for each fixation group was as follows: 13.9 ± 0.81 mm Hg for the anterior chamber lens group; 15.8 ± 1.77 mm Hg for the iris fixation group; and 17.6 ± 1.20 mm Hg for the transscleral fixation group. Analysis of variance demonstrated no significant difference in postoperative intraocular pressure between fixation groups ($P = .110$).

Nineteen of 41 eyes (46%) had glaucoma; preoperative glaucoma was present in 11 eyes (27%), and new onset of secondary glaucoma was diagnosed postoperatively in eight eyes (19%). Six of the eight cases of new-onset secondary glaucoma were from the transscleral fixation group. Uncontrolled glaucoma (range, 24.3 to 31.1 mm Hg) was present in three eyes (7%), all in the ciliary-sulcus fixation group. In five eyes (11.6%), evidence of postoperative peripheral anterior synechiae greater than one clock hour was found. Four of these five eyes were from the ciliary-sulcus fixation group, and one eye was from the iris fixation group; none had uncontrolled glaucoma. Three of the four eyes from the ciliary-sulcus group with peripheral anterior synechiae had synechiae in the approximate location of at least one of the polypropylene fixation sutures.

The mean postoperative central corneal thickness was 0.59 ± 0.01 mm (range, 0.41 to 0.73 mm). The central corneal thickness was 0.60 ± 0.02 mm (range, 0.52 to 0.72 mm) for the anterior chamber lens group, 0.59 ± 0.02 mm (range, 0.47 to 0.68 mm) for the iris fixation group, and 0.58 ± 0.01 (range, 0.41 to 0.73 mm) for the transscleral group. Analysis of variance

TABLE
DATA ON 41 PATIENTS*

CASE NO., AGE (YRS) SEX	FOLLOW-UP (MOS)	FIXATION GROUP	VISUAL ACUITY†		INTRAOCULAR PRESSURE (MM Hg)		CATARACT TO EDEMA INTERVAL (MOS)
			PREOPERATIVE	POSTOPERATIVE	PREOPERATIVE	POSTOPERATIVE	
1, 80, F	11	Anterior chamber	20/400	20/25	16	13	35
2, 83, F	15	Anterior chamber	20/200	20/50	8	17	96
3, 78, F	19	Anterior chamber	20/400	20/70	12	13.5	50
4, 86, F	18	Anterior chamber	HM	20/400	12	18	61
5, 82, F	21	Anterior chamber	CF	20/40	12	13.2	11
6, 64, F	9	Anterior chamber	CF	20/200	17	13.6	48
7, 77, F	17	Anterior chamber	20/400	20/70	16	16	48
8, 88, F	8	Anterior chamber	HM	20/400	9.1	8.9	156
9, 74, F	10	Anterior chamber	20/300	20/50	16	14	80
10, 81, F	14	Anterior chamber	20/40	20/70	19	12.4	17
11, 70, F	13	Iris	CF	20/200	19	10	20
12, 85, M	6	Iris	CF	CF	17	17	10
13, 53, M	15	Iris	20/300	20/60	27	16	221
14, 86, M	8	Iris	HM	HM	16	14	0
15, 76, F	26	Iris	20/200	20/25	13	10	48
16, 78, M	23	Iris	20/300	20/40	13	24	60
17, 77, M	24	Iris	20/400	CF	18	21.5	48
18, 75, F	16	Iris	CF	20/30	10	14	48
19, 54, F	16	Sulcus	20/400	20/50	19	15.9	22
20, 73, M	15	Sulcus	20/300	20/30	12	18	26
21, 73, M	22	Sulcus	CF	20/400	13	20.4	108
22, 82, F	15	Sulcus	CF	CF	14	16	24
23, 74, F	15	Sulcus	CF	20/50	12	13.3	44
24, 88, F	9	Sulcus	20/400	20/60	14	14	80
25, 83, F	5	Sulcus	HM	20/80	13	12	22
26, 81, M	12	Sulcus	20/70	20/40	9	31.1	52
27, 81, F	17	Sulcus	20/400	20/40	14	19	48
28, 73, F	16	Sulcus	CF	20/300	16	8.6	210
29, 80, M	16	Sulcus	HM	20/40	28	20	105
30, 76, F	9	Sulcus	CF	20/100	16	13	120
31, 77, F	7	Sulcus	20/300	20/50	16	16.1	28
32, 84, F	6	Sulcus	CF	20/400	12	18	24
33, 76, F	10	Sulcus	20/400	20/400	12	20.5	54
34, 83, F	15	Sulcus	CF	20/200	10.2	30.1	108
35, 70, F	5	Sulcus	CF	20/200	21	21.7	68
36, 73, F	6	Sulcus	CF	20/70	16	22.1	238
37, 71, F	11	Sulcus	20/80	20/40	16	15	29
38, 42, M	14	Sulcus	20/200	20/50	16	10	—
39, 81, M	14	Sulcus	CF	20/100	15	4.3	109
40, 71, F	16	Sulcus	20/200	20/40	6.4	10.7	158
41, 65, F	22	Sulcus	20/100	20/70	19	16	222

*An anterior chamber intraocular lens with closed loop was explanted in all but two cases. In Case 4 a posterior chamber intraocular lens of the original rigid J-loop type was explanted. In Case 16 an iris plane lens was explanted.

†CF indicates counting fingers, and HM indicates hand motions.

demonstrated no significant difference in central corneal thickness between the three fixation groups ($P = .666$).

The median preoperative visual acuity was 20/400 (range, 20/40 to hand motions). The median postoperative visual acuity was 20/70 (range, 20/25 to hand motions). Nine eyes (22%) had visual acuity of 20/40 or better; 24 eyes (58%) had visual acuity of 20/80 or better; and 27 eyes (66%) had visual acuity of 20/100 or better. Of the remaining 17 eyes with visual acuity of worse than 20/80, 16 (94%) had cystoid macular edema or atrophic macular degeneration. The median visual acuity for each fixation group was the following: 20/70 for the anterior chamber lens group, 20/100 for the iris fixation group, and 20/70 for the ciliary-sulcus fixation group. Analysis of variance (Kruskal-Wallis) demonstrated no significant difference in postoperative visual acuity between fixation groups ($P = .816$).

The number of eyes that attained visual acuity of 20/80 or better was also evaluated by fixation group: seven (70%) for the anterior chamber lens group, four (50%) for the iris fixation group, and 14 (61%) for the transscleral fixation group. Two eyes (5%) had postoperative visual acuity worse than the preoperative visual acuity. One patient had corneal graft astigmatism, and the second patient had advanced age-related macular degeneration and a failed graft secondary to immunologic rejection.

We used a Mantel-Haenszel chi-square test to compare postoperative visual acuity, which considered the degree of difficulty of each fixation technique. With the assumption that the surgical degree of difficulty was greatest for the ciliary-sulcus group and the least for the anterior chamber lens group, no association was found in postoperative visual acuity between fixation groups ($P = .387$).

Complications included immunologic graft failure in two of 41 eyes (5%). Two additional eyes had one graft reaction that resolved subsequently with frequent administration of topical prednisolone acetate 1%. Two additional complications from the transscleral group included one eye with a dislocated posterior chamber intraocular lens that was repositioned successfully and another eye with a conjunctival abscess surrounding an exposed polypropylene fixation suture that resolved after topical antibiotic therapy. The one fixation suture was removed without dislocation of the posterior chamber lens. One additional eye developed a

graft wound dehiscence upon suture removal that was resutured successfully.

Discussion

Treatment of pseudophakic corneal edema includes removal of a closed-loop anterior chamber intraocular lens, iris-plane lens, or dislocated lens at the time of keratoplasty. There is no agreement concerning the method of implantation of a new intraocular lens. An intraocular lens may be inserted in the anterior chamber angle or sutured to the iris or sclera. Advantages of an anterior chamber intraocular lens include ease of implantation and less manipulation. An anterior chamber lens, however, may be associated with progressive endothelial cell loss, peripheral anterior synechiae, and secondary glaucoma. Posterior chamber lens implantation requires greater manipulation and may prolong operating time, but this may be preferred in a patient with an abnormality of the anterior chamber angle.

Mean visual acuity varied between 20/44 and 20/400. The comparison of data is difficult because mean follow-up times, surgical techniques, and the number of patients varied considerably. Additionally, mean visual acuity may not be the most appropriate measurement of visual function, since a mean value of 20/44, for example, may not have clinical relevance. The mean may not reflect accurately the true central tendency of the sample population because of visual acuity measurements at the extreme of the visual acuity range. For example, four of 41 eyes (10%) had postoperative visual acuity measurements worse than 20/400, which represented the extreme of the postoperative range (20/40 to hand motions). We reported median visual acuity measurements because of greater clinical relevance and a more representative measurement of the central tendency of our sample population.

Lass and associates³ compared anterior chamber lenses to iris-fixed posterior chamber lenses. Postoperative visual acuity, intraocular pressure, and the percentage of endothelial cell loss were not significantly different. A prospective analysis of these fixation techniques would offer the best experimental model for evaluating postoperative results. We evaluated results from a single surgeon who performed three fixation techniques. Patients were not randomly allocated to each fixation group, and our

results may be biased. Preoperative characteristics, however, such as preoperative visual acuity, glaucoma, or iris status, were not considered in selecting an intraocular lens implantation technique.

All intraocular lenses explanted were of the closed-loop or iris-plane variety, except one rigid J-loop posterior chamber lens, which was associated with iris synechiae. Of 41 eyes, 38 (93%) had clear grafts with a median follow-up time of 15 months. Thirty-nine eyes (95%) had postoperative visual acuity that was the same or better than the preoperative visual acuity. The mean central corneal thickness for all patients was 0.59 ± 0.01 mm and was not significantly different between the three fixation groups.

Median preoperative (20/400) and postoperative (20/70) visual acuities were comparable with those of previous studies.⁴⁻⁶ We also compared median visual acuities from each fixation group: 20/70 for the anterior chamber lens group; 20/100 for the iris fixation group; and 20/70 for the transscleral ciliary-sulcus fixation group. Although the difference between the iris fixation group and the other fixation groups was three lines of Snellen visual acuity, analysis of variance demonstrated no significant difference. This apparent discrepancy illustrates the difficulty in comparing Snellen visual acuities for significant changes. Nonparametric analysis of variance (Kruskal-Wallis) was useful for comparison of visual acuity scores from three groups that were not normally distributed and of unequal sample size. A Mantel-Haenszel chi-square test was used to compare the three fixation techniques for degree of difficulty and found no association in postoperative visual acuity between fixation groups. Of 17 eyes with postoperative visual acuity worse than 20/200, 16 had cystoid macular edema or atrophic macular degeneration. Preoperative cystoid macular edema may be a risk factor for decreased vision after surgery. Evaluation of the retina before keratoplasty, however, was difficult because of corneal edema. Nevertheless, the median postoperative visual acuity (20/70) was much improved compared with preoperative levels (20/400).

Peripheral anterior synechiae of one clock hour or greater were detected postoperatively by slit-lamp biomicroscopy in five eyes, one from the iris fixation group and four from the transscleral ciliary-sulcus group. None had preoperative peripheral anterior synechiae. Three of the four eyes from the ciliary-sulcus group had synechiae adjacent to at least one of

the two polypropylene fixation sutures. The location of the fixation suture may have been related to the peripheral anterior synechiae. The eyes from the anterior chamber lens group showed no greater tendency to develop peripheral anterior synechiae. The increased number of eyes in the transscleral group with postoperative peripheral anterior synechiae may not be significant because of the few observations but warrants further investigation. Four of five eyes with synechiae had preoperative and postoperative glaucoma with intraocular pressure controlled medically; one eye developed postoperative secondary glaucoma controlled medically. Glaucoma may be a risk factor for developing peripheral anterior synechiae.

The mean preoperative intraocular pressure was 14.9 ± 0.68 mm Hg. The mean postoperative intraocular pressure of 16.6 ± 0.78 mm Hg was not significantly different. Analysis of variance demonstrated no significant difference between fixation groups. Eight eyes (19%) developed new onset of secondary glaucoma after the operation for a total of 19 eyes (46%) with medically treated glaucoma. Cycloablative or filtering procedures were not necessary to control intraocular pressure during the study period. Six cases of new-onset secondary glaucoma after keratoplasty developed in the transscleral fixation group, and one case developed in both the anterior chamber and the iris fixation groups. The frequency of secondary glaucoma in the transscleral group warrants further investigation.

Complications included immunologic graft reaction in four eyes with two leading to graft failure. Upon corneal suture removal, one graft had a wound dehiscence that was repaired promptly. A dislocated posterior chamber lens occurred in the transscleral fixation group. Another patient developed a conjunctival abscess surrounding an exposed polypropylene fixation suture. The suture was removed, and the abscess resolved with topical antibiotic therapy. Heilskov and associates⁷ believed exposure of a polypropylene fixation suture was the cause of postoperative endophthalmitis in their patient. The intraocular lens remained centrally located after suture removal. Stable fixation in the ciliary body may have resulted from a fibrous tissue reaction. Results of histopathologic studies of iris-fixated⁸ and transsclerally fixated⁹ posterior chamber lenses showed suspended lens loops rather than embedded or fixated loops in the ciliary sulcus. Accurate suture placement approximately 1.0 mm posterior to

the corneoscleral limbus may help direct lens loops into the ciliary sulcus.^{10,11} Sutures directed more posteriorly may result in inaccurate loop placement or accidental rupture of ciliary body vessels with consequent vitreous hemorrhage. No cases of vitreous hemorrhage or retinal detachment were found in our study.

The results of our study demonstrate no significant difference in postoperative visual acuity, central corneal thickness, and intraocular pressure when anterior chamber lenses and iris-sutured or transsclerally sutured posterior chamber lenses were implanted during intraocular lens exchange at the time of keratoplasty. No patients had greater than 90 degrees of peripheral anterior synechiae preoperatively. Therefore, our results cannot be applied to patients with prominent peripheral anterior synechiae. With this caveat in mind, our study supports the use of any one of these three fixation techniques with the expectation of similar results. Prospective randomized trials are needed to investigate these findings further.

References

1. Johnson, S. M.: Results of exchanging anterior chamber lenses with sulcus-fixated posterior chamber IOLs without capsular support in penetrating keratoplasty. *Ophthalmic Surg.* 20:465, 1989.
2. Insler, M. S., Kook, M. S., and Kaufman, H. E.: Penetrating keratoplasty for pseudophakic bullous keratopathy associated with semiflexible, closed-loop anterior chamber intraocular lenses. *Am. J. Ophthalmol.* 107:252, 1989.
3. Lass, J. H., DeSantis, D. M., Reinhart, W. J., Hossain, T. S., and Hom, D. L.: Clinical and morphometric results of penetrating keratoplasty with one-piece anterior-chamber or suture-fixated posterior-chamber lenses in the absence of lens capsule. *Arch. Ophthalmol.* 108:1427, 1990.
4. Busin, M., Brauweiler, P., Boker, T., and Spitznas, M.: Complications of sulcus-supported intraocular lenses with iris sutures, implanted during penetrating keratoplasty after intracapsular cataract extraction. *Ophthalmology* 97:401, 1990.
5. Zaidman, G. W., and Goldman, S.: A prospective study on the implantation of anterior chamber intraocular lenses during keratoplasty for pseudophakic and aphakic bullous keratopathy. *Ophthalmology* 97:757, 1990.
6. Heidemann, D. G., and Dunn, S. P.: Visual results and complications of transsclerally sutured intraocular lenses in penetrating keratoplasty. *Ophthalmic Surg.* 21:609, 1990.
7. Heilskov, T., Joondeph, B. C., Olsen, K. R., and Blankenship, G. W.: Late endophthalmitis after transscleral fixation of a posterior chamber intraocular lens. *Arch. Ophthalmol.* 107:1427, 1989.
8. Apple, D. J., Price, F. W., Gwin, T., Imkamp, E., Daun, M., Casanova, R., Hansen, S., and Carlson, A. N.: Sutured retropupillary posterior chamber intraocular lenses for exchange or secondary implantation. *Ophthalmology* 96:1241, 1989.
9. Lubniewski, A. J., Holland, E. J., Van Meter, W. S., Gussler, D., Parelman, J., and Smith, M. E.: Histologic study of eyes with transsclerally sutured posterior chamber intraocular lenses. *Am. J. Ophthalmol.* 110:237, 1990.
10. Davis, R. M., Campbell, D. M., and Jacoby, B. G.: Ciliary sulcus anatomical dimensions. *Cornea* 10:3, 1991.
11. Duffey, R. J., Holland, E. J., Agapitos, P. J., and Lindstrom, R. L.: Anatomic study of transsclerally sutured intraocular lens implantation. *Am. J. Ophthalmol.* 108:300, 1989.

The Clinical Characteristics of Pedigrees of Leber's Hereditary Optic Neuropathy With the 11778 Mutation

Nancy J. Newman, M.D., Marie T. Lott, M.A., and Douglas C. Wallace, Ph.D.

In a study of the phenotypic characteristics of pedigrees of Leber's hereditary optic neuropathy positive for the mitochondrial DNA mutation at position 11778, 28 of 49 pedigrees were represented by singleton cases. Seven families, including six singleton pedigrees, had maternal family members with a mixture of mutant and normal mitochondrial DNA (heteroplasmy). Seventy-two affected individuals from 43 families showed a male predominance of 81.9% (59/72) and ages of onset of visual loss ranging from 8 to 60 years. The time interval between affected eyes averaged 1.8 months; the duration of progression of visual loss in each eye averaged 3.7 months. Visual acuity was 20/200 or worse in 107 of 109 (98.2%) eyes. Telangiectatic microangiopathy, disk pseudoedema, or vascular tortuosity, ophthalmoscopic features believed to be classic of Leber's hereditary optic neuropathy, were noted in 30 of 52 patients. Visual-evoked responses were typically absent or abnormal. Electrocardiograms, fluorescein angiograms, cerebrospinal fluid analyses, brain computed tomography, and magnetic resonance imaging were usually normal. There were no consistent neurologic or systemic illnesses associat-

ed with these Leber's pedigrees. In many cases, the diagnosis would not have been suspected because of the absence of a compatible family history, typical clinical profile, or ophthalmoscopic appearance. Genetic analysis showed the mitochondrial DNA mutation at position 11778, which established the diagnosis of Leber's hereditary optic neuropathy and has allowed for a broader view of the clinical features of this disease.

LEBER'S hereditary optic neuropathy is a maternally inherited disease that results in bilateral visual loss, primarily in young men. In 1988, we identified a mitochondrial deoxyribonucleic acid (DNA) replacement mutation at nucleotide position 11778 in nine of 11 families with members in whom the clinical diagnosis of Leber's hereditary optic neuropathy was made.¹ This mutation, in which guanine is replaced by adenine, converts the highly conserved 340th amino acid of reduced nicotinamide adenine dinucleotide (NADH) dehydrogenase subunit 4 from an arginine to a histidine. This same mutation has been confirmed in approximately 40% to 60% of pedigrees worldwide with Leber's hereditary optic neuropathy.¹⁻¹³

Heteroplasmy for the 11778 mutation (the coexistence of mutant and normal mitochondrial DNA within the same individual) has been demonstrated in affected and unaffected members of Leber's optic neuropathy families.^{5,7,8,14-16} In some pedigrees there has been rapid segregation toward homoplasmy for the mutation.^{5,7,8} There is some speculation that the relative proportion of mutant mitochondrial DNA content in individuals, and perhaps within tissues of the same individual, may affect phenotypic expression.

The clinical manifestations associated specifically with the 11778 mutation have not yet been described. Herein we report 49 independent Leber's pedigrees harboring the 11778 mutation and summarize the phenotypic characteristics of a single genotype.

Accepted for publication April 2, 1991.

From the Departments of Ophthalmology (Dr. Newman), Neurology (Drs. Newman and Wallace), and the Center for Genetics and Molecular Medicine (Dr. Newman, Ms. Lott, and Dr. Wallace), Emory University School of Medicine, Atlanta, Georgia. This study was supported in part by a departmental grant from Research to Prevent Blindness, Inc. (Dr. Newman); by National Institutes of Health grant N521328 and a Muscular Dystrophy Clinical Research grant (Dr. Wallace); and by the Clinical Research Center of Emory University School of Medicine, supported by National Institutes of Health grant M01-RR-00039. This study was presented in part at the International Neuro-Ophthalmology Symposium in Winchester, England, June 27, 1990.

Reprint requests to Nancy J. Newman, M.D., Neuro-Ophthalmology Unit, Emory Eye Center, 1327 Clifton Rd. N.E., Atlanta, GA 30322.

GENOTYPE AND FAMILY HISTORY OF PATIENTS WITH LEBER'S OPTIC NEUROPATHY*

PEDIGREE NO. [†]	11778 MUTATION [‡]	MULTIPLE FAMILY MEMBERS	FAMILY SUSPECT FUNDUS [§]	INCIDENTAL DISEASE [¶]
1	100%	Y	Y	—
4	100%	N	Y	Supraventricular tachycardia
5	100%	Y	—	—
6	100%	Y	—	—
8	100%	N	—	—
9	100%	N	N	—
10	Heteroplasmic	N	—	—
11	100%	N	—	—
12	100%	N	—	—
13	Heteroplasmic	Y	—	Deafness
15	100%	N	N	Supraventricular tachycardia; muscle weakness
16	100%	N	Y	—
18	100%	Y	Y	Peripheral neuropathy
19	100%	N	—	—
21	100%	N	N	—
25	100%	N	N	—
26	100%	Y	—	Seizures; deafness
30	100%	Y	Y	—
31	100%	N	—	Peripheral neuropathy
35	Heteroplasmic	N	—	Peripheral neuropathy; deafness
36	100%	Y	—	—
37	Heteroplasmic	N	N	—
38	100%	N	N	—
39	Heteroplasmic	N	—	Multiple sclerosis
40	100%	Y	—	—
44	100%	Y	N	Juvenile diabetes mellitus; muscular dystrophy; hysterical blindness
47	100%	N [§]	N	Short stature and optic atrophy
49	100%	Y	Y	—
55	100%	N	N	Polio
58	100%	Y	—	—
60	Heteroplasmic	N	N	Developmental immaturity
64	100%	N	—	—
65	Heteroplasmic	N [§]	N	Unilateral optic atrophy; multiple sclerosis
67	100%	N	—	Mental retardation
70	100%	Y	—	—
71	100%	N	—	—
72	100%	N	—	—
73	100%	N	—	—
74	100%	Y	—	—
75	100%	Y	—	—
76	100%	N	N	—
77	100%	N	—	—
78	100%	N	N	—
1F	100%	Y	—	—
2F	100%	Y	—	—
3F	100%	Y	—	—
4F	100%	Y	—	—
5F	100%	Y	—	—
1T	100%	Y	—	—

*Y indicates yes; N indicates no. The number of positive pedigrees was 49; singleton pedigrees, 28 (57.1%); and heteroplasmic pedigrees, 7 (14.3%).

[†]F indicates Finnish; T indicates Tasmanian.

[‡]100% indicates guanine to adenine mutation present at 11778 in essentially homoplasmic state as visualized by ethidium bromide staining.

[§]Other family members with visual loss secondary to undefined optic neuropathy.

[§]Suspect fundus: disk edema, pseudoedema, hyperemia, telangiectasias, or vascular tortuosity seen in at least one asymptomatic family member examined.

[¶]Incidental disease indicates reported neurologic or systemic illness in either probands or maternal relatives.

Material and Methods

Blood samples from patients and family members who were suspected of having Leber's hereditary optic neuropathy were referred to our laboratory. Blood was also tested from 80 unrelated random control individuals. Informed consent was obtained from all subjects and controls. Two samples (Cases 31.01 and 74.01) were obtained as air-dried blood spots. For the rest of the cases, blood was collected in sodium heparin. As described previously,⁸ 200 to 300 μ l of whole blood was removed for immediate DNA extraction and lymphocytes from the remainder were transformed with Epstein-Barr virus to establish lymphoblastoid cell lines. The DNA was extracted by using either an anion-exchange affinity column⁸ (Qiagen, Inc., Studio City, California) or by standard proteinase K/phenol-chloroform methods.¹⁷

The 11778 mutation eliminates a site where a restriction endonuclease, Sfa N1 (New England Biolabs, Beverly, Massachusetts), normally cuts the mitochondrial DNA, thus providing a direct molecular diagnostic test.¹ A DNA fragment was prepared by using the polymerase chain reaction between forward and reverse oligonucleotide primers (Microchemical Facility, Emory University, Atlanta, Georgia) located at nucleotide positions 11141 to 11158 and 12576 to 12557. This 1435 base pair fragment, encompassing the nucleotide position 11778 Leber's hereditary optic neuropathy marker, was digested with one unit of Sfa N1 at 37 C for 16 hours. The digested DNA was subjected to electrophoresis on 1.4% tris-borate agarose gels. Normal mitochondrial DNA-generated fragments of 679, 638, and 119 base pairs (nucleotide positions 11778 to 12456, 11141 to 11778, and 12456 to 12576, respectively). Mutant mitochondrial DNAs had the 679 and 638 base pair fragments fused into 1317 base pairs (nucleotide positions 11141 to 12456), while also retaining the common 119 base pair fragment. Heteroplasmic samples disclosed four fragments after Sfa N1 digestion: 1317 base pairs (representing Leber's hereditary optic neuropathy), 679 and 638 base pairs (representing normal), and 119 base pairs. Most cases were confirmed by digestion with the restriction enzyme Mae 3 (Boehringer Mannheim, Indianapolis, Indiana). The 11778 guanine to adenine mutation creates a Mae 3 site, thus

generating a 124 base pair and 131 base pair doublet (delineated by nucleotide positions 11651 to 11775 and 11775 to 11906) when the Leber's mutation is present or a 255 base pair fusion fragment for normal, uncut, mitochondrial DNAs.^{9,11} Mae 3 digestion of the test DNA also generates 613, 511, and 57 base pair fragments common to both DNA types. In all cases, a sample containing only water was subjected to the polymerase chain reaction and enzymatic digestion to ensure that no contaminating carryover DNA was present in the reagents used.

Pedigrees were included in this study if at least one member in the maternal lineage tested positive for the 11778 mitochondrial DNA mutation. Survey sheets requesting specific clinical information were sent to all referring physicians. Individuals within these families were included in the clinical analysis if they had experienced visual loss unexplained by other ocular or neurologic disease, and if patient sex and age at onset of visual dysfunction were known. Clinical information was collected from review of survey sheets, medical records, and by telephone conversations with referring physicians, patients, and family members.

Specific historical questions included the sex of the affected individual, the age at onset of visual loss, associated symptoms at the time of acute loss, the time interval between affected eyes, and the duration of progression of visual loss in each eye. When possible, detailed medical histories and family histories were obtained, with special attention given to ophthalmic, neurologic, and cardiac disease. Any known exposure to environmental toxins, tobacco, alcohol, and drugs was noted. Features of the ophthalmic examination of particular interest included the ultimate visual acuity, color vision, visual field defects, and ophthalmoscopic appearance (especially during the acute phase of visual loss). The results of ancillary testing, such as fluorescein angiograms, electroretinograms, visual-evoked responses, brain computed tomography, brain magnetic resonance imaging, cerebrospinal fluid analysis, and electrocardiograms, were tabulated when available.

Results

A total of 49 independent pedigrees had at least one family member test positive for the 11778 mutation in blood samples (Table 1).

TABLE 2
CLINICAL SUMMARY OF AFFECTED INDIVIDUALS WITH THE 11778 MUTATION*

CASE NO.	SEX	AGE OF ONSET (YRS)	ONSET INTERVAL (MO)	PROGRESSION OF LOSS (MO)		ULTIMATE VISUAL ACUITY		CENTRAL VISUAL FIELD DEFECTS?		SUSPECT FUNDUS?†	
				RE	LE	RE	LE	RE	LE	RE	LE
1.01	M	45	1	2	1	5/200	1/200	Y	Y	Y	Y
1.02	M	21	0	4	4	HM	LP	Y	Y	N	N
1.03	M	20	0	1	1	LP	LP	—	—	N	N
1.04	M	24	0	2	2	CF 2ft	CF 5ft	Y	Y	N	N
1.05	F	50	0	1.5	1	CF 4ft	20/200	Y	Y	Y	Y
1.06	F	36	0	3	3	CF 2ft	CF 2ft	Y	Y	N	N
1.07	F	53	3	3	3	20/400	CF 2ft	—	—	Y	Y
1.08	M	44	2	2	2	NLP	NLP	—	—	Y	Y
1.09	M	35	NA	6	NA	CF 3ft	NA	—	NA	N	NA
4.01	M	28	0	1	1	—	—	—	—	—	—
5.01	M	16	—	—	—	—	—	—	—	—	—
5.02	M	17	—	—	—	—	—	—	—	—	—
6.01	M	24	—	—	—	20/400	20/1000	Y	Y	—	—
6.02	M	17	—	—	—	—	—	—	—	—	—
8.01	M	32	0	7	7	2/200	3/200	Y	Y	N	N
9.01	M	18	0	2	2	CF 1ft	10/200	Y	Y	Y	Y
10.01	M	18	2	1.5	2	CF 3ft	CF 3ft	Y	Y	Y	Y
11.01	M	25	0	7	7	4/200	4/200	Y	Y	Y	Y
12.01	M	28	2	—	6	HM	CF	Y	Y	Y	Y
13.01	M	15	—	—	—	<20/200	<20/200	Y	Y	Y	Y
13.02	M	10	—	—	—	—	—	—	—	—	—
15.01	F	25	5	5	3	10/200	8/200	Y	Y	Y	Y
16.01	M	8	—	3	3	CF 1ft	20/50	Y	Y	Y	Y
18.01	M	34	0.5	2	2	1/200	1/200	Y	Y	Y	Y
18.02	F	24	—	—	—	1/200	1/200	—	—	—	—
19.01	M	21	1.5	3	3	10/200	2/200	Y	Y	Y	Y
21.01	M	26	9	4	4	CF 1ft	CF 1ft	Y	Y	Y	Y
25.01	F	28	0	10	10	HM	HM	Y	Y	Y	Y
26.01	M	23	5	4	8	CF 3ft	CF 2ft	Y	Y	N	N
26.02	M	30	—	—	—	—	—	—	—	—	—
26.03	M	15	—	—	—	—	—	—	—	—	—
30.01	M	60	0	3	3	20/200	5/200	Y	Y	N [‡]	N [‡]
30.02	M	51	0	2	2	10/200	5/200	Y	Y	N	N
30.03	M	25	—	—	—	—	—	—	—	—	—
31.01	M	20	5	—	—	1/200	1/200	Y	Y	Y	Y
35.01	M	58	0	24	24	CF	CF	Y	Y	Y	Y
36.01	M	54	0	4	4	3/200	3/200	Y	Y	Y	Y
36.02	M	19	—	—	—	—	—	—	—	—	—
37.01	M	34	6	4	4	20/400	20/400	Y	Y	Y	Y
38.01	M	18	0	3	3	20/200	CF 2ft	Y	Y	Y	Y
39.01	M	20	—	—	—	—	—	—	—	—	—
40.01	M	12	0	2	2	20/50	20/200	Y	Y	N	N
40.02	M	23	0	—	—	—	—	—	—	—	—
44.01	F	9	0	1	1	20/200 [†]	20/200 [†]	Y	Y	N [‡]	N [‡]
44.02	F	37	0	—	—	CF 1ft	CF 1.5ft	Y	Y	N	N
44.03	M	37	—	—	—	20/500	20/500	—	—	—	—
44.04	F	31	—	—	—	20/800	20/800	—	—	—	—
47.01	M	14	0	1	1	20/400	20/400	Y	Y	Y	Y

Continued on pg 754

TABLE 2 (Continued)
CLINICAL SUMMARY OF AFFECTED INDIVIDUALS WITH THE 11778 MUTATION*

CASE NO.	SEX	AGE OF ONSET (YRS)	ONSET INTERVAL (MO)	PROGRESSION OF LOSS (MO)		ULTIMATE VISUAL ACUITY		CENTRAL VISUAL FIELD DEFECTS?		SUSPECT FUNDUS?†	
				RE	LE	RE	LE	RE	LE	RE	LE
49.01	M	18	6	6	6	CF 1ft	CF 1ft	Y	Y	Y	Y
49.02	M	20	—	—	—	—	—	—	—	—	—
49.03	M	60	—	—	—	—	—	—	—	—	—
49.04	F	47	—	3	3	CF 1ft	CF 1ft	Y	Y	Y	Y
55.01	M	18	0	3	3	HM	HM	Y	Y	N	N
58.01	M	30	0	0.75	0.75	10/200	CF 1ft	Y	Y	Y	Y
58.02	F	29	1	2	2	10/200	CF 4ft	Y	Y	Y	Y
60.01	M	12	NA	NA	3	NA	5/200†	NA	Y	NA	N [‡]
64.01	M	23	8	0	2	CF 6ft	CF 2ft	Y	Y	Y	Y
65.01	M	21	0	6	6	15/200	10/200	Y	Y	Y	Y
67.01	M	24	0	7	7	CF 2ft	CF 2ft	Y	Y	N	N
70.01	M	17	6	3	3	CF 6ft	CF 4ft	Y	Y	N	N
70.02	M	21	—	—	—	—	—	—	—	—	—
70.03	M	20	—	—	—	—	—	—	—	—	—
71.01	F	54	2	—	1	CF 1ft	2/200	Y	Y	N [‡]	N [‡]
72.01	M	16	6	3	1	CF 2ft	CF 2ft	Y	Y	N	Y
73.01	M	50	0.5	4	2	4/200	20/200	Y	Y	Y	Y
74.01	F	19	NA	—	—	NA	CF	NA	Y	NA	N [‡]
74.02	M	19	6	—	—	—	—	—	—	N [‡]	N [‡]
75.01	M	35	—	—	—	7/200	7/200	—	—	Y	Y
75.02	M	50	0	—	—	20/200	20/200	—	—	—	—
76.01	M	10	0	—	—	20/400	3/200	Y	Y	N [‡]	N [‡]
77.01	M	28	—	0.25	0.25	CF 1ft	CF 1ft	Y	Y	N [‡]	N [‡]
78.01	M	15	8	6	—	20/400†	CF 4ft	Y	Y	N [‡]	N [‡]

*Cases are numbered with family number to left of decimal, individual number to right of decimal. Y indicates Yes; N, No; HM, hand motion; CF, count fingers; LP, light perception; NLP, no light perception. NA indicates data not available because of other intervening factors (traumatic injury in Case 1.09; persistent hyperplastic primary vitreous/cataract in Case 60.01; visual loss still in initial stages at time of publication in Case 74.01.)

†Eyes that had spontaneous improvement in visual acuity.

‡Suspect fundus: disk edema, pseudoeedema, hyperemia, telangiectasias, or vascular tortuosity.

§The fundus was examined at the time of initial visual loss.

None of 80 control blood samples were positive for the mutation. Seven families (14.3%) (No. 10, 13, 35, 37, 39, 60, and 65) demonstrated some degree of heteroplasmy for the mutation within blood. Three of these showed varying amounts of heteroplasmy in different tissues within the same individual (No. 10, 35, and 39).⁸

Twenty-eight families (57.1%) are represented by a single proband with visual loss and have no other members with a history of visual dysfunction compatible with Leber's hereditary optic neuropathy or unexplained by other ocular or neurologic disease. Two of these 28 pedigrees (No. 47 and 65), however, each contain a

family member with visual loss secondary to an undefined, possibly congenital, optic neuropathy. In pedigree No. 47, the maternal aunt of the proband had short stature and was incidentally noted at the age of 5 years to have visual acuity of 20/200 in both eyes and optic atrophy. In family No. 65, a maternal half-sister had visual acuity of 20/1,000 and optic atrophy in the left eye, discovered at age 4 years. The right eye had visual acuity of 20/20 and remained normal both functionally and by ophthalmoscopic examination into adulthood.

The pedigrees with more than one affected family member are indicated (Table 1). The clinical characteristics of six pedigrees (five

Finnish and one Tasmanian) have either been described previously in some detail¹⁸⁻²³ or are in the process of being reported by others. Within the 43 remaining families, historical information was available on 72 individuals (Table 2). Twelve patients (Cases 1.01, 1.02, 1.04, 1.05, 1.06, 1.07, 1.08, 1.09, 11.01, 40.01, 60.01, and 78.01) were personally interviewed and examined at Emory University.

The male-to-female ratio among patients was 59:13 (81.9% male). There were two sets of twins (monozygotic brothers and a dizygotic brother and sister), with only one male affected in each pair. The age at onset of visual loss for the first eye ranged from 8 to 60 years old, with a mean of 27.6 years. Forty-nine patients (68.1%) were 16 to 37 years old at onset. Thirteen (18.1%) were older, ten (13.9%) younger. The time interval between affected eyes was documented in 47 patients and ranged from simultaneous onset to nine months (mean, 1.8 months). Simultaneous onset was reported in 26 of 47 cases (55.3%). Two affected individuals had monocular visual loss from other causes, one (Case 60.01) from congenital persistent hyperplastic primary vitreous and cataract, the other (Case 1.09) from ocular trauma. One 19-year-old woman (Case 74.01) with an affected brother just recently lost vision in the left eye. The right eye has yet to become involved. The duration of progression of visual loss within each eye was reported in 87 eyes, ranging from sudden and complete to 24 months. The mean time to stabilization was 3.7 months (3.2 months if the one outlier, Case 35.01, was removed from the calculation).

Five of our patients recalled having other symptoms at the time of acute visual loss. One patient (Case 21.01) had headaches; one patient (Case 70.01) had eye pain; and one patient (Case 38.01) said he had the "flu." Phenomena, described as flashes of light, color, or both, occurred in two of our patients (Cases 8.01 and 15.01). Two patients (Cases 37.01 and 78.01) had transient worsening of vision with exercise. Superimposed episodes of monocular visual loss lasting seconds to days or even weeks with subsequent return to baseline visual acuity occurred in one patient (Case 15.01). The presumably unaffected maternal cousin of the patient described in Case 4.01 had an episode of bilateral diminution in vision at age 30 years that lasted ten hours.

Information on the ultimate visual acuity was available for 109 eyes. The range was from no light perception to 20/50, but visual acuity was

20/200 or worse in all (98.2%) except two eyes. Four other eyes have shown subsequent spontaneous improvement in visual acuity. With Case 44.01 both eyes improved from 20/200 to 20/40 after several months. With Case 60.01 the left eye improved from 5/200 to 20/20 suddenly 2½ years after initial visual loss. The left eye in one patient (Case 78.01) improved from 20/400 to 20/30 after one year. The visual fields performed on 47 patients were uniformly described as showing central or cecocentral defects.

In 1973, Smith, Hoyt, and Susac²⁴ described the classic ophthalmoscopic appearance of patients with Leber's hereditary optic neuropathy and acute visual loss: circumpapillary telangiectatic microangiopathy, swelling of the nerve fiber layer around the disk (pseudoedema), and absence of staining on fluorescein angiography. Ophthalmoscopic abnormalities other than optic atrophy were considered "suspect" in our study for the characteristic Leber's fundus appearance if photographs or ophthalmologists' descriptions disclosed disk edema, pseudoedema, hyperemia, telangiectatic microangiopathy, or vascular tortuosity. At least one of these findings was present in 59 of 101 eyes (30 of 52 patients). Photographs were available on only a few patients and ophthalmoscopic documentation was not consistently complete enough to comment on the incidence of the full typical Leber's ophthalmoscopic picture as described by Smith, Hoyt, and Susac.²⁴ Of the 22 patients whose ophthalmoscopic examinations did not show even suspect findings, only nine were examined at the time of acute visual loss. At that time, these fundi were normal; later there was optic disk pallor.

Ophthalmoscopic examination of at least one asymptomatic family member disclosed suspect findings in six of 19 families examined (Table 1). Two of these six pedigrees contained only a single affected family member. All but one of the 13 examined families without asymptomatic fundus changes were also singleton pedigrees.

Seventeen of 37 affected individuals were users of tobacco. Twenty-one of 36 patients used alcohol, three heavily (Cases 1.08, 19.01, and 70.01). Only one patient was reported as a chronic recreational drug abuser (Case 58.02). Significant exposure to a toxic waste site containing measured high levels of Mirex, phthalic acid, benzene, and carbon disulfide was documented in one patient (Case 16.01), solvent exposure in another (Case 35.01).

Three of our patients (Cases 18.01, 31.01, and 35.01) were described as having peripheral neuropathy (Table 1). One patient (Case 15.01) had nonspecific muscle weakness, and another (Case 55.01) was said to have had "polio" as an infant. When one patient (Case 60.01) had initial acute visual loss at age 12 years, he was also noted to have growth and sexual immaturity. Diabetes mellitus was diagnosed in a 9-year-old girl (Case 44.01) at the time of her visual loss. One singleton woman (Case 15.01) had a history of supraventricular tachycardia, as did the unaffected maternal cousin of the patient designated Case 4.01.

Isolated maternally related family members of our patients had supraventricular tachycardia (pedigree No. 4), seizures (No. 26), mental retardation (No. 67), short stature and bilateral optic atrophy (No. 47), unilateral optic atrophy (No. 65), muscular dystrophy (No. 44), hysterical blindness (No. 44), and multiple sclerosis (No. 39 and 65) (Table 1). Deafness was reported in the maternal grandfather, five of seven maternal uncles, and one maternal aunt in pedigree No. 13, and in maternally related family members in pedigrees No. 26 and 35.

Electrocardiogram results were reported on 17 affected individuals. Fourteen of these were normal (Cases 1.01, 1.02, 1.04, 1.05, 1.06, 1.07, 1.08, 9.01, 10.01, 19.01, 37.01, 60.01, 70.01, and 71.01). One electrocardiogram showed supraventricular tachycardia (Case 15.01), another a short QT interval (Case 44.02), and a third premature ventricular contractions (Case 49.01). Brain computed tomography was reported as normal for the 22 patients on whom they were performed (Cases 1.05, 1.08, 8.01, 11.01, 12.01, 13.01, 15.01, 19.01, 21.01, 31.01, 35.01, 37.01, 38.01, 40.01, 58.01, 58.02, 60.01, 64.01, 65.01, 71.01, 73.01, and 74.01). Sixteen of 18 brain magnetic resonance images were also normal (Cases 1.05, 1.06, 9.01, 10.01, 11.01, 15.01, 16.01, 19.01, 25.01, 35.01, 44.01, 47.01, 60.01, 71.01, 73.01, and 78.01). One magnetic resonance study in a 60-year-old man (Case 30.01) had several small bright T₂ white matter signals of unclear significance. The magnetic resonance image of a 34-year-old man (Case 37.01) showed white matter lesions and his cerebrospinal fluid analysis disclosed oligoclonal banding. Spinal fluid was normal in 11 other patients (Cases 1.02, 1.05, 8.01, 13.01, 11.01, 19.01, 25.01, 38.01, 44.01, 47.01, and 65.01). Visual-evoked responses were either absent or abnormal with prolonged latencies, and diminished amplitudes in 14 of 15 affected

individuals (Cases 1.05, 1.06, 6.02, 9.01, 11.01, 19.01, 25.01, 30.01, 38.01, 47.01, 60.01, 71.01, 72.01, and 78.01). Visual-evoked responses in one woman with visual loss (Case 58.02) were reported as having normal latency and amplitude. One brainstem auditory evoked response study was normal (Case 78.01). Ten of 11 standard flash electroretinograms were normal (Cases 1.05, 1.06, 6.02, 16.01, 25.01, 35.01, 58.02, 60.01, 71.01, and 72.01). One electroretinogram was reported as showing abnormal scotopic function (Case 36.01). A pattern electroretinogram on one patient (Case 11.01) was nonreactive in both eyes. Fluorescein angiograms were reported on eight patients (Cases 1.05, 9.01, 19.01, 21.01, 38.01, 49.01, 65.01, and 78.01). One angiogram (Case 19.01) demonstrated disk leakage. An electroencephalogram was performed on one patient and it was normal (Case 21.01). Three muscle biopsy results were reported. One was considered normal (Case 1.02), one inconclusive (Case 44.01), and a third was thought to have nonspecific myopathic changes (Case 25.01). A skin biopsy was normal (Case 25.01) and one orbital ultrasound disclosed small optic nerves (Case 38.01). An exploratory craniotomy with visualization of the chiasm and intracranial optic nerves found no abnormalities in one patient (Case 1.02).

Discussion

To clarify the relationship between genotype and phenotype, we attempted to define the 11778 mitochondrial DNA mutation phenotype by compiling the clinical data from all such pedigrees referred to us (Figure). Consistent with previous clinical reports of Leber's hereditary optic neuropathy, we observed a predominance of affected males, 82% in our study compared with 77% to 90% in European, North American, and Australian pedigrees.^{21,25-32} By contrast, in Japan the male predominance is less marked, males representing 58% of cases.³³ The average age at onset of visual loss in our 11778-positive patients was 27.6 years, with 68% of our cases falling between 16 and 37 years of age. Our patients' average age is slightly higher than that calculated by van Senus at 24.4 years for men and 22 years for women.²⁸

About half of our patients with 11778 mutation (26 of 47) reported simultaneous onset of bilateral visual loss (55.3%). This probably in-

PATIENT SEX

Males: 59 / 72 patients (81.9%)

Females: 13 / 72 patients (18.1%)

AGE OF ONSET

Average age: 27.6 years

Range: 8 - 60 years

ONSET INTERVAL

Simultaneous: 26 / 47 patients (55.3%)

Interval average: 1.8 months

Interval range: simultaneous to 9 months

PROGRESSION OF VISUAL LOSS (87 eyes)

Average: 3.7 months

Range: 0 - 24 months

VISUAL ACUITY

Better than 20/200: 2 / 109 eyes (1.8 %)

20/200 or worse: 107 / 109 eyes (98.2 %)

OPHTHALMOSCOPIC EXAMINATION

Suspect fundus: 59 / 101 eyes (58.4 %);
30 / 52 patients (57.7 %)

Nonsuspect fundus: 42 / 101 eyes (41.6 %);
22 / 52 patients (42.3 %)

Figure (Newman, Lott, and Wallace). Summary statistics of Leber's hereditary optic neuropathy patients with the 11778 mutation (72 individuals in 43 families). Suspect fundus indicates presence of disk edema, pseudoeedema, hyperemia, telangiectasias or vascular tortuosity.

cludes both cases of true simultaneous onset and those in which involvement of the first eye went unrecognized. Equally high incidences of coincident onset have been reported by van Senus, 64.1%,²⁸ and Asseman, 70%.²⁷ In cases of noncoincident visual loss, the second eye is

usually involved within months of the first. Unless we consider as an example of Leber's hereditary optic neuropathy the maternal half-sister of our patient designated in Case 65.01 with unilateral optic neuropathy incidentally discovered at age 4 years, our patients did not have intervals longer than nine months. The duration of progression of visual loss in each eye has been described in the literature as anything from sudden and rapid to greater than two years.^{21,27,28,32} Stabilization in most patients occurs by three months,^{27,28} a figure that parallels our mean of 3.7 months.

Other symptoms at the time of acute visual loss were reported rarely by our patients. Two of our patients reported phenomena similar to the light and color sensations described by many of van Senus's patients.²⁸ Two other patients had transient worsening of vision with exercise, a symptom consistent with Uhthoff's symptom in Leber's hereditary optic neuropathy.^{19,24,34} The cause or significance of the more prolonged episodes of visual loss reported by one of our patients and the maternal cousin of another remains unclear.

Overall, patients with the 11778 mutation had a poor visual outcome, with only two of 109 eyes (1.8%) testing better than 20/200 (Figure). In previous reports of Leber's hereditary optic neuropathy, visual acuities ranged from no light perception to 20/20.^{24,27,28,32-35} In most reported cases visual acuity deteriorated to Snellen acuities of worse than 20/200, and only 8% of van Senus's patients²⁸ had visual acuities better than 20/200 at the time of stabilization after acute visual loss. We do not know how long after stabilization our patients' visual acuities were obtained. In some cases, a nadir may have been missed with subsequent unrecognized improvement. It is likely, however, that most of these patients had vision assessed during the acute phase and the data may actually underestimate the potential for recovery. Only three of our patients have had documented improvement in their visual acuity (Cases 44.01, 60.01, and 78.01). Spontaneous recovery of some vision in at least one eye was reported in 45.2% of patients in van Senus's pedigrees; in 25% of cases this improvement was as good as 20/50 in one eye.²⁸ Other series reported spontaneous improvement in usually a smaller percentage of patients, although often years after the acute phase.^{26,28,32,34,36} Holt, Miller, and Harding⁵ noted recovery of useful vision in members of four Leber's families negative for the 11778 mutation and in none of four Leber's

families positive for the mutation. Whether our data confirm a poorer visual prognosis for patients with Leber's hereditary optic neuropathy and the 11778 mutation requires longer follow-up.

Following the report by Smith, Hoyt, and Susac,²⁴ which describes the classic ophthalmoscopic appearance in patients with Leber's hereditary optic neuropathy, Nikoskelainen and associates^{18,21,22,37} noted typical peripapillary microangiopathy in all of their acutely symptomatic Leber's patients, some of their pre-symptomatic patients, and in asymptomatic maternal relatives. Lopez and Smith³⁸ described two patients with Leber's hereditary optic neuropathy who did not exhibit the typical Leber's fundus changes even during the acute phase, but who had maternal relatives who did, which helped to establish the correct diagnosis.

Ocular fundus descriptions were provided in 52 of our 72 cases. Even allowing extremely liberal criteria for inclusion as suspect fundi, 22 of these 52 patients (42.3%) had either normal fundi or isolated optic disk pallor. Hence, they had no ophthalmoscopic findings suggestive of Leber's hereditary optic neuropathy as opposed to other causes of bilateral optic atrophy. Similarly, Smith and colleagues¹² described one patient positive for the 11778 mutation who had only equivocal ophthalmoscopic findings, although his mother had definite circumpapillary microangiopathy.

Only nine of the 22 patients lacking suspect fundi were examined at the time of acute visual loss. One of these nine patients (Case 44.01) belonged to a family with several affected family members; we do not have information regarding their acute ophthalmoscopic appearance. A second patient (Case 30.01) also had relatives with visual loss, as well as an asymptomatic brother with peripapillary telangiectasias. Two siblings (Cases 74.01 and 74.02), both without suspect fundi at the time of acute visual loss, were the only affected members of their family. The other five patients without suspect fundi at the time of acute visual loss were singleton cases: 10-, 12-, and 15-year-old boys (Cases 76.01, 60.01, and 78.01), a 28-year-old man (Case 77.01), and a 54-year-old woman (Case 71.01). Results of the ophthalmoscopic examinations of maternal relatives of Cases 60.01, 76.01, and 78.01 were normal (Table 1). Hence, there may be nothing in the family history, initial ophthalmologic examination, or examination of maternal relatives of patients

with the 11778 mutation to suggest a diagnosis of Leber's hereditary optic neuropathy. Ophthalmoscopic examination alone cannot identify individuals harboring the 11778 mutation.

Most of the neurologic and systemic abnormalities reported in our 11778 mutation patients and their families were minor and not necessarily related to this particular mitochondrial mutation (Table 1). Families with more severe neurologic syndromes and bilateral optic neuropathies considered identical to Leber's hereditary optic neuropathy have been reported.^{39,40} However, neither the California pedigree with dystonia and basal ganglial lesions⁴⁰ nor the Australian family with movement disorders, spasticity, and encephalopathy³⁹ test positive for the 11778 mutation.^{1,41}

Two of our pedigrees had a maternally related family member with the diagnosis of multiple sclerosis. Another patient (Case 37.01) had white matter lesions on magnetic resonance imaging and oligoclonal bands in the cerebrospinal fluid, nonspecific paraclinical findings suggestive of multiple sclerosis. Disease clinically indistinguishable from multiple sclerosis has previously been noted in Leber's pedigrees.^{19,34,42}

Among our 43 pedigrees, one singleton woman and the unaffected maternal cousin of a singleton man had a history of supraventricular tachycardia. An electrocardiogram performed on the patient designated Case 44.02 showed a short QT interval. Cardiac conduction abnormalities, specifically pre-excitation syndromes, have been associated with Leber's hereditary optic neuropathy in numerous pedigrees.^{18,20,43} A more directed study of electrocardiograms from multiple family members would be necessary before conclusions regarding concurrent cardiac abnormalities can be drawn.

The results of ancillary testing on our patients were also similar to those discussed in the literature. All of the brain computed tomographic scans and most magnetic resonance images performed were normal. Kermode and associates⁴⁴ performed magnetic resonance imaging on 13 affected Leber's patients and found no brain lesions. Using short-time inversion recovery sequences to image the optic nerves in eight patients, Kermode and associates⁴⁴ noted increased signal within at least one optic nerve in each patient. We are unaware if any of the patients in our series had short-time inversion recovery sequences performed. A patient with 11778-positive Leber's hereditary optic neu-

ropathy described by Smith and associates¹² had distended, fluid-filled optic nerve sheaths demonstrated by computed tomography, magnetic resonance imaging, and orbital ultrasound.

As would be expected, visual-evoked responses in patients affected by Leber's hereditary optic neuropathy may be absent or show increased latencies, decreased amplitudes.^{19,35,45} Standard flash electroretinograms are typically normal in patients with Leber's hereditary optic neuropathy.^{27,28,36} Our data support this, although a 54-year-old man in our series had an electroretinogram suggesting abnormal scotopic function. This is interesting in light of some data of van Senns in which dark adaptation (also a function of the rods) was abnormal in a significant proportion of his patients.²⁸

The determinants of expression in Leber's hereditary optic neuropathy remain speculative. In those pedigrees positive for the 11778 mutation, not all of the maternal relatives at risk will develop visual loss. In some families, heteroplasmy may be partially responsible for the clinical expression of the disease. Progressive enrichment of the mutant mitochondrial DNA content from one generation to the next has been demonstrated in several 11778-positive pedigrees^{6,7,8,16} and correlated in some with disease phenotype.^{5,7,8} Seven of our pedigrees were heteroplasmic, six of them represented by singleton cases. This is likely an underestimate of the incidence of heteroplasmy, since in some singleton cases, blood samples were received only from the affected individual and not from maternal relatives. If enrichment of the content of the mutation helps to determine phenotypic expression, then it is possible that the proband could be 100% mutant while unaffected siblings or members of prior generations are heteroplasmic. In a previous publication,⁸ we demonstrated this progressive enrichment and relation to phenotype in two pedigrees (No. 10 and 39). We have found this also to be the case in two generations of singleton family No. 37. It is theoretically possible that varying degrees of heteroplasmy among tissues could result in different proportions of mutant mitochondrial DNA in the optic nerves and retinas of individuals who test similarly for the mutation in blood.

Other factors likely contribute to phenotypic expression. The significant male predominance in Leber's hereditary optic neuropathy could reflect X-linked nuclear-encoded modification

of mitochondrial DNA expression. An attempt to link Leber's hereditary optic neuropathy with markers on the X chromosome in the Tasmanian family in our series was unsuccessful,²³ but Vilkki and associates⁴⁶ recently suggested X-linkage to the liability of phenotypic expression in Leber's pedigrees both with and without the 11778 mutation.

Systemic illnesses, nutritional deficiencies, and exposure to substances toxic to mitochondrial energy production have all been proposed as potential precipitating factors, presumably because of their potential to cause respiratory stress.^{15,34,47} One singleton case in our series, a boy with onset of visual loss at age 8 years, had documented exposure to a toxic waste site. In pedigree No. 44, a family with multiple affected members with visual dysfunction onset typically in the 30s, a 9-old-girl (Case 44.01) had visual loss in the setting of six months of unrecognized diabetes mellitus. Her systemic illness may have placed a significant stress on mitochondrial energy production.

The clinical characteristics of our affected individuals harboring the 11778 mutation are not dissimilar from those previously reported among members of Leber's families. This is partly a result of the wide clinical variability of this disease even among members of the same pedigree. What is remarkable about our series, however, is the large proportion of pedigrees with only a single affected family member. To some degree, this reflects a referral bias for those cases without an established familial diagnosis. Previously, the diagnosis of Leber's hereditary optic neuropathy in patients without a family history for the disease was made tentatively by recognition of the classic manifestation in a young man with the typical ophthalmoscopic appearance or by recognition of this ophthalmoscopic appearance in asymptomatic maternal relatives.^{24,36,38,48} Three of our singleton patients (Cases 15.01, 25.01, and 71.01) were women. Five singletons (Cases 16.01, 47.01, 60.01, 76.01, and 78.01) were younger than 16 years old; three (Cases 35.01, 71.01, and 73.01) were older than 49 years. Eight individuals without family history (Cases 8.01, 55.01, 60.01, 67.01, 71.01, 76.01, 77.01, and 78.01) never had even suspect fundus findings documented. The maternal relatives of four of these eight patients were examined and they, too, had nonsuspect fundi. Genetic testing for the 11778 mitochondrial DNA mutation established the diagnosis of Leber's hereditary optic

neuropathy under clinical circumstances that otherwise would not have suggested the disease.

Given the atypical characteristics of some of our singleton cases, the question arises as to whether some of the test results are false-positive, and these cases are not actually examples of Leber's hereditary optic neuropathy. The original report by Wallace and associates¹ included 45 independent, unrelated controls. At least 180 additional control subjects negative for the mutation have since been described in the literature.^{5,6,49} The 80 negative controls in this study bring the total to over 300 controls without a single false-positive test. Interestingly, given the number of singleton pedigrees documented, it is reasonable to suspect that a so-called "false-positive" test will occur in time, but to prove this "falsehood" may need several generations.

The availability of a simple genetic test for the 11778 mitochondrial DNA mutation to establish the diagnosis of Leber's hereditary optic neuropathy has far reaching implications for patients, their families, and their physicians. It may obviate the need for extensive and expensive ancillary testing, provide important information for genetic and family counseling, expand our view of what constitutes the clinical phenotype of Leber's hereditary optic neuropathy, allow for clinical comparison with other genotypic abnormalities, and establish a genetically homogeneous database for future studies. The last point is of particular importance for any therapeutic trials and may identify individuals at risk before visual loss or involvement of the fellow eye.

ACKNOWLEDGMENT

The following individuals referred patients for mitochondrial DNA analysis and provided information essential to this study: Kwame Anyane-Yeboah, M.D.; James H. Bates, M.D.; Lyn Beck, M.D.; F.R.C.S.; Jerome H. Becker, M.D.; William C. Bromley, M.D.; Lori A. Callis, M.D.; John E. Carter, M.D.; Russell P. Edwards, M.D.; Robert P. Erickson, M.D.; Steven E. Feldon, M.D.; Merry Ferre, M.S.; William A. Fletcher, M.D.; H. Allan Gardner, M.D.; R. J. M. Gardner, M.D.; Rose Giardine, M.S.; James A. Goodwin, M.D.; Sheron Gustafson, M.S.; Jesse I. Halpern, M.D.; Donald R. Johns, M.D.; Haig H. Kazazian, M.D.; Gregory S. Kosmorsky, D.O.; Simmons Lessell, M.D.; Ivor S. Levy, M.D.,

F.R.C.S.; Ruth Lieberfarb, M.D.; B. Lorenz, M.D.; Eric F. Maas, M.D.; Nancy M. Newman, M.D.; Jeffrey W. Nichols, M.D.; Eeva Nikoskelainen, M.D.; Stephen C. Pollock, M.D.; Joseph F. Rizzo, M.D.; Alfredo A. Sadun, M.D.; Robert C. Sergott, M.D.; Allan Shanske, M.D.; Patrick A. Sibony, M.D.; Michael E. Sulewski, M.D.; Robert L. Tomsak, M.D.; and Melba Wilson, Ph.D.

References

1. Wallace, D. C., Singh, G., Lott, M. T., Hodge, J. A., Schurr, T. G., Lezza, A. M. S., Elsas, L. J., II, and Nikoskelainen, E. K.: Mitochondrial DNA mutation associated with Leber's hereditary optic neuropathy. *Science* 242:1427, 1988.
2. Singh, G., Lott, M. T., and Wallace, D. C.: A mitochondrial mutation as a cause of Leber's hereditary optic neuropathy. *N. Engl. J. Med.* 320:1300, 1989.
3. Hotta, Y., Hayakawa, M., Saito, K., Kanai, A., and Nakajima, A.: Diagnosis of Leber's optic neuropathy by means of polymerase chain reaction amplification. *Am. J. Ophthalmol.* 108:601, 1989.
4. Yoneda, M., Tsuji, S., Yamauchi, T., Inuzuka, T., and Miyatake, T.: Mitochondrial DNA mutation in a family with Leber's hereditary optic neuropathy. *Lancet* 1:1076, 1989.
5. Holt, I. J., Miller, D. H., and Harding, A. E.: Genetic heterogeneity and mitochondrial DNA heteroplasmy in Leber's hereditary optic neuropathy. *J. Med. Genet.* 26:739, 1989.
6. Vilkkii, J., Savontaus, M. L., and Nikoskelainen, E. K.: Genetic heterogeneity in Leber hereditary optic neuroretinopathy revealed by mitochondrial DNA polymorphism. *Am. J. Hum. Genet.* 45:206, 1989.
7. Bolhuis, P. A., Bleeker-Wagemakers, E. M., Ponne, N. J., Van Schooneveld, M. J., Van den Bogert, C., and Tabak, H. F.: Rapid shift in genotype of human mitochondrial DNA in a family with Leber's hereditary optic neuropathy. *Biochem. Biophys. Res. Commun.* 170:994, 1990.
8. Lott, M. T., Voljavec, A. S., and Wallace, D. C.: Variable genotype of Leber's hereditary optic neuropathy patients. *Am. J. Ophthalmol.* 109:625, 1990.
9. Stone, E. M., Coppinger, J. M., Kardon, R. H., and Donelson, J.: Mae III positively detects the mitochondrial mutation associated with type I Leber's hereditary optic neuropathy. *Arch. Ophthalmol.* 108:1417, 1990.
10. Morris, M. A.: Mitochondrial mutations in neuro-ophthalmological diseases. A review. *J. Clin. Neuro-Ophthalmol.* 10:159, 1990.
11. Johns, D. R.: Improved molecular-genetic diagnosis of Leber's hereditary optic neuropathy. *N. Engl. J. Med.* 323:1488, 1990.

12. Smith, J. L., Tse, D. T., Byrne, S. F., Johns, D. R., and Stone, E. M.: Optic nerve sheath distention in Leber's optic neuropathy and the significance of the "Wallace mutation." *J. Clin. Neuro-Ophthalmol.* 10:231, 1990.
13. Johns, D. R.: The molecular genetics of Leber's hereditary optic neuropathy. *Arch. Ophthalmol.* 108:1405, 1990.
14. Shoffner, J. M., IV, and Wallace, D. C.: Oxidative phosphorylation diseases. Disorders of two genomes. *Adv. Hum. Genet.* 19:267, 1990.
15. Newman, N. J., and Wallace, D. C.: Mitochondria and Leber's hereditary optic neuropathy. *Am. J. Ophthalmol.* 109:726, 1990.
16. Vilkki, J., Savontaus, M. L., and Nikoskelainen, E. K.: Segregation of mitochondrial genomes in a heteroplasmic lineage with Leber hereditary optic neuroretinopathy. *Am. J. Hum. Genet.* 47:95, 1990.
17. Ausubel, F. M., Brent, R., Kingston, R. E., Moore, D. D., Seidman, J. G., Smith, J. A., and Struhl, K.: *Current Protocols in Molecular Biology*. New York, John Wiley & Sons, 1989, p. 2.2.1.
18. Nikoskelainen, E. K., Savontaus, M. L., Wanne, O. P., Katila, M. J., and Nummelin, K. U.: Leber's hereditary optic neuroretinopathy, a maternally inherited disease. A genealogic study in four pedigrees. *Arch. Ophthalmol.* 105:665, 1987.
19. Nikoskelainen, E., Sogg, R. L., Rosenthal, A. R., Friberg, T. R., and Dorfman, L. J.: The early phase in Leber hereditary optic atrophy. *Arch. Ophthalmol.* 95:969, 1977.
20. Nikoskelainen, E., Wanne, O., and Dahl, M.: Pre-excitation syndrome and Leber's hereditary optic neuroretinopathy. *Lancet* 1:969, 1985.
21. Nikoskelainen, E., Hoyt, W. F., and Nummelin, K.: Ophthalmoscopic findings in Leber's hereditary optic neuropathy. II. The fundus findings in the affected family members. *Arch. Ophthalmol.* 101:1059, 1983.
22. Nikoskelainen, E., Hoyt, W. F., Nummelin, K., and Schatz, H.: Fundus findings in hereditary optic neuroretinopathy. III. Fluorescein angiographic studies. *Arch. Ophthalmol.* 102:981, 1984.
23. Chen, J.-D., Cox, I., and Denton, M. J.: Preliminary exclusion of an X-linked gene in Leber optic atrophy by linkage analysis. *Hum. Genet.* 82:203, 1989.
24. Smith, J. L., Hoyt, W. F., and Susac, J. O.: Ocular fundus in acute Leber optic neuropathy. *Arch. Ophthalmol.* 90:349, 1973.
25. Leber, T.: Ueber hereditäre und congenital-angelegte sehnervenleiden. *Graefes Arch. Ophthalmol.* 17:249, 1891.
26. Lundsgaard, R.: Leber's disease. A genealogic, genetic and clinical study of 101 cases of retrobulbar optic neuritis in 20 Danish families. *Acta Ophthalmol.* 21(suppl.):300, 1944.
27. Asseman, R.: La maladie de Leber. Etude clinique et genetique a propos de 86 cas examines, thesis. Lille, France, 1958.
28. Van Senus, A. H. C.: Leber's disease in the Netherlands. *Doc. Ophthalmol.* 17:1, 1963.
29. Seedorf, T.: Leber's disease. *Acta Ophthalmol.* 46:4, 1968.
30. Seedorf, T.: The inheritance of Leber's disease. A genealogical follow-up study. *Acta Ophthalmol.* 63:135, 1985.
31. Bell, J.: Hereditary optic atrophy (Leber's disease). In Pearson, K. (ed.): *The Treasury of Human Inheritance*, vol. 2, part 4. Cambridge, Cambridge University Press, 1931, pp. 325-423.
32. Bird, A., and McEachern, D.: Leber's hereditary optic atrophy in a Canadian family. *Can. Med. Assoc. J.* 61:376, 1949.
33. Imachi, J.: Neuro-surgical treatment of Leber's optic atrophy and its pathogenetic relationship to arachnoiditis. In Brunett, J. R., and Barbeau, A. (eds.): *Progress in Ophthalmology*, vol. 2. (Proceedings of the Second International Congress of Neuro-Genetics and Neuro-Ophthalmology). Montreal, Excerpta Medica, 1967, pp. 121-127.
34. Miller, N. R.: The hereditary optic neuropathies. Monosymptomatic hereditary optic neuropathies. Leber's optic neuropathy. In Miller, N. R. (ed.): *Walsh and Hoyt's Clinical Neuro-Ophthalmology*. Baltimore, Williams and Wilkins, 1982, pp. 311-317.
35. Carroll, W. M., and Mastaglia, F. L.: Leber's optic neuropathy. A clinical and visual evoked potential study of affected and asymptomatic members of a six generation family. *Brain* 102:559, 1979.
36. Lessell, S., Gise, R. L., and Krohel, G. B.: Bilateral optic neuropathy with remission in young men. Variation on a theme by Leber? *Arch. Neurol.* 40:2, 1983.
37. Nikoskelainen, E., Hoyt, W. F., and Nummelin, K.: Ophthalmoscopic findings in Leber's hereditary optic neuropathy. I. Fundus findings in asymptomatic family members. *Arch. Ophthalmol.* 100:1597, 1982.
38. Lopez, P. F., and Smith, J. L.: Leber's optic neuropathy. New observations. *J. Clin. Neuro-Ophthalmol.* 6:144, 1986.
39. Wallace, D. C.: A new manifestation of Leber's disease and a new explanation for the agency responsible for its unusual pattern of inheritance. *Brain* 93:121, 1970.
40. Novotny, E. J., Singh, G., Wallace, D. C., Dorfman, L. J., Louis, A., Sogg, R. L., and Steinman, L.: Leber's disease and dystonia. A mitochondrial disease. *Neurology* 36:1053, 1986.
41. Howell, N., and McCullough, D.: An example of Leber hereditary optic neuropathy not involving a mutation in the mitochondrial ND4 gene. *Am. J. Hum. Genet.* 47:629, 1990.
42. De Weerd, C. J., and Went, L. N.: Neurological studies in families with Leber's optic atrophy. *Acta Neurol. Scand.* 47:541, 1971.
43. Rose, F. C., Bowden, A. N., and Bowden, P. M. A.: The heart in Leber's optic atrophy. *Br. J. Ophthalmol.* 54:388, 1970.
44. Kermode, A. G., Moseley, I. F., Kendall, B. E.,

Miller, D. H., MacManus, D. G., and McDonald, W. I.: Magnetic resonance imaging in Leber's optic neuropathy. *J. Neurol. Neurosurg. Psychiatry* 52:671, 1989.

45. Livingstone, I. R., Mastaglia, F. L., Howe, J. W., and Aherne, G. E. S.: Leber's optic neuropathy. Clinical and visual evoked response studies in asymptomatic and symptomatic members of a 4-generation family. *Br. J. Ophthalmol.* 64:751, 1980.

46. Vilkkki, J., Ott, J., Savontaus, M.-J., Aula, P., and Nikoskelainen, E. K.: Optic atrophy in Leber hereditary optic neuroretinopathy is probably deter-

mined by an X-chromosomal gene closely linked to DXS7. *Am. J. Hum. Genet.* 48:486, 1991.

47. Nikoskelainen, E.: New aspects of the genetic, etiologic, and clinical puzzle of Leber's disease. *Neurology* 34:1482, 1984.

48. Nikoskelainen, E., Nummelin, K., and Savontaus, M.-L.: Does sporadic Leber's disease exist? *J. Clin. Neuro-Ophthalmol.* 8:225, 1988.

49. Johns, D. R., and Berman, J.: Alternative, simultaneous complex I mitochondrial DNA mutations in Leber's hereditary optic neuropathy. *Biochem. Biophys. Res. Commun.* 174:1324, 1991.

OPHTHALMIC MINIATURE

I, too, was busy, trying to reason out how he was aware of the existence of so intangible a thing as a shadow. If it were his eyeballs only that were affected, or if his optic nerve were not wholly destroyed, the explanation was simple. If otherwise, then the only conclusion I could reach was that the sensitive skin recognized the difference of temperature between shade and sunshine. Or, perhaps,—who can tell?—it was that fabled sixth sense which conveyed to him the loom and feel of an object close at hand.

Jack London, *The Sea Wolf*
New York, Bantam Books, 1986, p. 216

AMERICAN JOURNAL OF OPHTHALMOLOGY®

FRANK W. NEWELL, *Publisher and Editor-in-Chief*
Suite 1415, 435 North Michigan Ave., Chicago, Illinois 60611

EDITORIAL BOARD

Thomas M. Aaberg, *Atlanta*
Jules Baum, *Boston*
William M. Bourne, *Rochester*
Ronald M. Burde, *New York*
Fred Ederer, *Bethesda*
Frederick T. Fraunfelder, *Portland*
Michael A. Kass, *St. Louis*
Steven G. Kramer, *San Francisco*
Irving H. Leopold, *Irvine*

Robert Machemer, *Durham*
Nancy M. Newman, *San Francisco*
Don H. Nicholson, *Miami*
Edward W. D. Norton, *Miami*
Deborah Pavan-Langston, *Boston*
Allen M. Putterman, *Chicago*
Dennis Robertson, *Rochester*
Merlyn M. Rodrigues, *Baltimore*
Stephen J. Ryan, *Los Angeles*

Jerry A. Shields, *Philadelphia*
M. Bruce Shields, *Durham*
Ronald E. Smith, *Los Angeles*
Bruce E. Spivey, *San Francisco*
Bradley R. Straatsma, *Los Angeles*
H. Stanley Thompson, *Iowa City*
E. Michael Van Buskirk, *Portland*
Gunter K. von Noorden, *Houston*

Published monthly by the OPHTHALMIC PUBLISHING COMPANY
Suite 1415, 435 North Michigan Avenue, Chicago, Illinois 60611

Directors

Edward W. D. Norton, *President*
Bradley R. Straatsma, *Vice President*
Frank W. Newell, *Secretary and Treasurer*

Bruce E. Spivey
Thomas M. Aaberg
Michael A. Kass

PERSPECTIVES

Lacrimal Gland Epidermal Growth Factor Production and the Ocular Surface

Steven E. Wilson, M.D.

Aqueous tear secretion has long been attributed to the main and accessory lacrimal glands and is an important function that is essential for maintaining the integrity of the ocular surface. Previous studies, however, demonstrated that the lacrimal gland contributes other components to tears, including peroxidase,^{1,2} amylase,³ beta-hexosaminidase,³ and retinol.⁴ Recently, investigations devoted to the production of epidermal growth factor suggested more provocative regulatory functions for the lacrimal gland relating to maintenance of the ocular surface and the control of wound healing.

Epidermal growth factor was first identified as a component of mouse tears by Tsutsumi, Tsutsumi, and Takami.⁵ Subsequent reports have confirmed that human tears also contain epidermal growth factor.^{6,7} Immunologic identi-

fication of epidermal growth factor-like protein within the lacrimal gland provided the first evidence that the lacrimal gland synthesizes epidermal growth factor.^{8,9} Immunologic detection, however, offered only suggestive evidence that the lacrimal gland actually produced epidermal growth factor, since the identified protein could have localized to the lacrimal tissue by sequestration rather than synthesis. Additionally, there are other proteins known to contain epidermal growth factor-like sequences that could be identified by anti-epidermal growth factor immunoglobulin. Recently, however, epidermal growth factor precursor messenger RNA has been identified in mouse,¹⁰ rabbit (unpublished data), and human (unpublished data) lacrimal gland by sensitive molecular biologic techniques. Since the epidermal

growth factor precursor messenger RNA molecule specifies the sequence for the epidermal growth factor precursor protein, these studies provided conclusive evidence that lacrimal gland actually synthesizes the growth factor.

Although disparate reports continue to appear, a number of studies have reported that epidermal growth factor can stimulate proliferation or migration of ocular surface epithelium.¹¹⁻¹⁵ The presence of epidermal growth factor in tears and identification of epidermal growth factor receptors on the surface of corneal and conjunctival epithelial cells^{9,16} suggest the possibility of exocrine participation by the lacrimal gland in ocular surface maintenance and wound healing. Additional autocrine, paracrine, or endocrine roles cannot, however, be excluded. Thus far, epidermal growth factor is the only growth factor that has been shown to be synthesized by the lacrimal gland. However, other lacrimal gland-produced growth factors probably will be identified.

The lacrimal gland is innervated by sympathetic, parasympathetic, and peptidergic nerve fibers.¹⁷ Alpha-adrenoreceptor stimulation has been shown to increase secretion of peroxidase from lacrimal gland cells *in vitro*.¹⁸ A reflex arc connecting the efferent innervation of the cornea with the afferent innervation of the lacrimal gland, analogous to reflex aqueous tear secretion in response to corneal stimulation, could provide a precisely controlled system for increasing epidermal growth factor (and perhaps other regulatory factors) in response to ocular surface injury.

Clinicians are frequently frustrated by the poor correlation between aqueous tear production and the extent of ocular surface disease in keratoconjunctivitis sicca.¹⁹ The poor sensitivity of tests used to detect keratoconjunctivitis sicca, such as the Schirmer test, which quantitates aqueous tear production, has been well documented.²⁰ Perhaps deficient epidermal growth factor or other regulatory factor production by the lacrimal gland, independent of aqueous tear production, is instrumental in the pathogenesis of the disease in at least a subgroup of patients with dry eye syndrome. Topical administration of the appropriate factor might offer significant therapeutic benefits for these individuals.

Alterations in lacrimal gland growth factor production could also occur after ophthalmic division trigeminal nerve lesions and contribute to decreased epithelial cell mitosis,²¹ de-

creased wound healing,²² and decreased epithelial thickness,²³ which are characteristic of neurotrophic corneal ulcers. Similarly, one could hypothesize that abnormal lacrimal gland growth factor production could have a role in persistent corneal epithelial defects.

If a nervous system regulatory arc exists between the ocular surface and the lacrimal gland, one might expect augmented lacrimal epidermal growth factor or other growth factor production by the lacrimal gland in response to corneal injury. Depending on the timing of exogenous epidermal growth factor administration relative to endogenous epidermal growth factor production by the lacrimal gland, epidermal growth factor receptors on the epithelial cells could be occupied and, therefore, little additional effect from the exogenous epidermal growth factor might be noted. Alternatively, epithelial epidermal growth factor receptor down-regulation produced by the sporadic administration of topical epidermal growth factor⁹ could theoretically interfere with a system that features precisely controlled release of endogenous epidermal growth factor. Rational design of protocols for exogenous epidermal growth factor administration to facilitate wound healing will only be possible when we achieve a more thorough understanding of endogenous epidermal growth factor production by the lacrimal gland and epidermal growth factor receptor regulation by the epithelial cells of the ocular surface.

Finally, if lacrimal gland epidermal growth factor production makes a significant contribution to ocular surface wound healing, then it may be possible to modify more directly the wound healing response through the administration of pharmacologic agents that either increase or decrease epidermal growth factor production, depending on the clinical situation. Thus, in patients with corneal epithelial defects it might be advantageous to stimulate lacrimal epidermal growth factor production. After refractive surgical procedures, either stimulation or inhibition of lacrimal gland epidermal growth factor production could be appropriate depending on the initial response to surgery and the effect of epidermal growth factor on stromal remodeling and epithelial hyperplasia.

In retrospect, considering the level of interest in corneal wound healing and growth factors, it seems ironic that the discovery of lacrimal gland epidermal growth factor occurred only recently. This new appreciation for the once

lowly lacrimal gland may lead to insights with far-reaching clinical and research implications.

From the Department of Ophthalmology, University of Texas Southwestern Medical Center, Dallas, Texas.

Reprint requests to Steven E. Wilson, M.D., Department of Ophthalmology, University of Texas Southwestern Medical Center, 5323 Harry Hines Blvd., Dallas, TX 75235.

References

1. Essner, E.: Localization of endogenous peroxidase in rat exorbital lacrimal gland. *J. Histochem. Cytochem.* 19:216, 1971.
2. Herzog, V., and Miller, F.: The localization of endogenous peroxidase in the lacrimal gland of the rat during postnatal development. *J. Cell. Biol.* 53:662, 1972.
3. Thörig, L., van Haeringen, N. J., and Wijnngaards, G.: Comparison of enzymes of tears, lacrimal gland fluid, and lacrimal gland tissue in the rat. *Exp. Eye Res.* 38:605, 1984.
4. Ubels, J. L., Foley, K. M., and Rismondo, V.: Retinol secretion by the lacrimal gland. *Invest. Ophthalmol. Vis. Sci.* 27:1261, 1986.
5. Tsutsumi, O., Tsutsumi, A., and Takami, O.: Epidermal growth factor-like, corneal wound healing substance in mouse tears. *J. Clin. Invest.* 81:1067, 1988.
6. Ohashi, Y., Motokura, M., Kinoshita, Y., Mano, T., Wananabe, H., Kinoshita, S., Manabe, R., Oshiden, K., and Yanaihara, C.: Presence of epidermal growth factor in human tears. *Invest. Ophthalmol. Vis. Sci.* 30:1879, 1989.
7. van Setten, G. B., Viinikka, L., Tervo, T., Pesonen, K., Tarkkanen, A., and Perheentupa, J.: Epidermal growth factor is a constant component of normal human tear fluid. *Graefes Arch. Clin. Exp. Ophthalmol.* 227:184, 1989.
8. Tervo, K., van Setten, G. B., Virtanen, I., Tarkkanen, A., and Tervo, T.: The lacrimal gland is the source of epidermal growth factor in tear fluid. An immunochemical study in rats. *ARVO abstracts. Supplement to Invest. Ophthalmol. Vis. Sci. Philadelphia, J. B. Lippincott, 1990, p. 45.*
9. Steinemann, T. L., Thompson, H. W., Maroney, K. M., Palmer, C. H., Henderson, L. A., Malter, J. S., Clarke, D., Bromberg, B., Kunkle, M., and Beuerman, R. W.: Changes in epithelial epidermal growth factor receptor and lacrimal gland EGF concentration after corneal wounding. *ARVO abstracts. Supplement to Invest. Ophthalmol. Vis. Sci. Philadelphia, J. B. Lippincott, 1990, p. 55.*
10. Kasayama, S., Ohba, Y., and Oka, T.: Expression of the epidermal growth factor gene in mouse lacrimal gland. Comparison with that in the submandibular gland and kidney. *J. Mol. Endocrinol.* 4:31, 1990.
11. Frati, L., Daniele, L., Delogu, A., and Covelli, I.: Selective binding of epidermal growth factor and its specific effects on the epithelial cells of the cornea. *Exp. Eye Res.* 14:135, 1972.
12. Savage, C. R., Jr., and Cohen, S.: Proliferation of corneal epithelium induced by epidermal growth factor. *Exp. Eye Res.* 15:361, 1973.
13. Gospodarowicz, D., Mescher, A. L., Brown, K. D., and Birdwell, C. R.: The role of fibroblast growth factor and epidermal growth factor in the proliferative response of the corneal and lens epithelium. *Exp. Eye Res.* 25:631, 1977.
14. Petroutsos, G., Courty, J., Guimaraes, R., Poulquien, Y., Barritault, D., Plouet, J., and Courtois, Y.: Comparison of the effects of EGF, pEGF, and EDGF on corneal epithelium wound healing. *Curr. Eye Res.* 3:593, 1984.
15. Watanabe, K., Nakagawa, A., and Nishida, T.: Stimulatory effects of fibronectin and EGF on migration of corneal epithelial cells. *Invest. Ophthalmol. Vis. Sci.* 28:205, 1987.
16. Couch, J., Cullen, P., Casey, T., and Fabre, J.: Epidermal growth factor receptor sites in the human and monkey eye. *ARVO abstracts. Supplement to Invest. Ophthalmol. Vis. Sci. Philadelphia, J. B. Lippincott, 1988, p. 86.*
17. Botelho, S. Y., Hisada, M., and Fuenmayor, N.: Functional innervation of the lacrimal gland in the cat. *Arch. Ophthalmol.* 76:581, 1966.
18. Thörig, L., Van Haeringen, N. J., Timmermans, P. B. M. W. M., and van Zwieten, P. A.: Alpha adreno-receptor control of peroxidase secretion from rat lacrimal gland cells in vitro. *Exp. Eye Res.* 35:29, 1982.
19. Lemp, M. A.: Recent developments in dry eye management. *Ophthalmology* 94:1299, 1987.
20. Lucca, J. A., Nunez, J. N., and Farris, R. L.: A comparison of diagnostic tests for keratoconjunctivitis sicca. Lactoplate, Schirmer, and tear osmolality. *CLAO J.* 16:109, 1990.
21. Sigelman, S., and Friedenwald, J. S.: Mitotic and wound-healing activities of the corneal epithelium. *Arch. Ophthalmol.* 52:46, 1954.
22. Beuerman, R. W., and Schimmelpfennig, B.: Sensory denervation of the rabbit cornea affects epithelial properties. *Exp. Neurol.* 69:196, 1980.
23. Alper, M. G.: The anesthetic eye. An investigation of changes in the anterior ocular segment of the monkey caused by interrupting the trigeminal nerve at various levels along its course. *Trans. Am. Ophthalmol. Soc.* 73:324, 1975.

How Safe Are Disposable Soft Contact Lenses?

Thomas John, M.D.

Bacterial keratitis and corneal ulceration have been recognized as vision-threatening complications that may be related to soft contact lenses, especially extended-wear lenses. Disposable soft contact lenses were introduced because it was thought that frequent replacement would minimize or eliminate infectious complications of soft contact lens wear. Corneal infection is the most dreaded complication associated with the wearing of soft contact lenses. Thus, if no corneal infection occurs with disposable soft contact lenses, they can be considered relatively safe. Now that the disposable soft contact lens is a reality and is slowly increasing in popularity, one needs to ask, "How safe are disposable soft contact lenses?"

When conventional soft contact lenses were introduced initially in the United States, they were considered to be relatively safe, and some were approved by the Food and Drug Administration for continuous wear for up to one month. These conventional extended-wear soft contact lenses provided clear vision during the waking hours, and they quickly became popular.

In the mid-1980s, with the increasing use of conventional soft contact lenses for daily wear and especially for extended wear, potential soft contact lens-related complications began to be apparent, of which *Pseudomonas* corneal ulceration was the most feared. *Pseudomonas aeruginosa* was identified as the most common organism related to the use of both daily-wear and extended-wear soft contact lenses. At that time, it was also known that cleaning of these lenses did not remove all of the lens surface coatings and deposits. There was an increase in infectious complications related to conventional soft contact lens wear and to the inability to clean these lenses completely. It was in this setting that disposable soft contact lenses were developed. Frequent changes to new lenses were thought to solve the problem of corneal infections related to the wearing of conventional soft contact lenses.

Ten patients with culture-proved infectious keratitis and corneal ulceration associated with the use of disposable soft contact lenses have been described in published reports.¹⁻⁷ Of these ten infections, nine were bacterial and one was

caused by *Acanthamoeba*. In these cases, the most common organism cultured was *P. aeruginosa*, which accounted for seven cases of corneal infections.¹⁻⁷ Is history repeating itself? Is the situation the same with disposable soft contact lenses as what happened with conventional soft contact lenses in the mid-1980s?

Of six patients on whom data were available, three did not follow instructions for discarding the lenses and used their disposable soft contact lenses for more than the recommended maximum period of two weeks (Table). Disposable soft contact lenses are similar in gross appearance to the conventional daily-wear and extended-wear soft contact lenses, which some of the patients may have used before changing to disposable lenses. Therefore, individuals may have found it difficult to discard a new lens every two weeks as prescribed. Instead, they may have used these lenses longer and thus used fewer lenses in an attempt to decrease the annual cost. Hence, there is a potential for noncompliance, which may contribute to corneal complications.

According to a recent survey, wearers of disposable soft contact lenses account for 6.4% of all contact lens wearers.⁸ This number is expected to increase in the immediate future. If the present rate of noncompliance continues, more corneal complications may result. Therefore, it is important that those who dispense disposable soft contact lenses instruct their patients to discard the lenses after two weeks of use.

Currently, three types of disposable soft contact lenses are available in the United States: Acuvue (Vistakon Co., Johnson and Johnson), introduced in January 1987; SeeQuence (Bausch and Lomb), introduced in June 1988; and NewVues (CIBA Vision), introduced in April 1989. The water content of these lenses ranges from 38% (SeeQuence) to 58% (Acuvue). Weissman and associates⁹ stated that "disposable lenses are just as likely to cause hypoxic stress to the cornea as other reusable hydrogel contact lenses of similar composition and water content." Hence, with regard to corneal stress secondary to contact lens wear, disposable soft contact lenses are not better than conventional lenses of similar composition and hydration and can lead to corneal

TABLE
REPORTED CASES OF CULTURE-PROVEN *PSEUDOMONAS* KERATITIS/CORNEAL ULCERATION RELATED TO WEAR OF DISPOSABLE SOFT CONTACT LENSES*

STUDY	AGE (YRS), SEX	COMPLIANCE	TIME LENS WAS FIRST DISCARDED (DAYS)	VISUAL ACUITY		ULCER SITE	ULCER SIZE (MM)	SOURCE OF INFECTION
				INITIAL	FINAL			
Killinsworth and Stern ¹	18, M	Yes	7	CF at 1 foot	CF	Peripheral	5.0	Unknown
Kersher ²	19, NA	No	21	20/400	NA	Central	1.0	Unknown
Rabinowitz and Pflugfelder ³	50, F	No	7-9	NA	NA	Peripheral	1.0	Sterile aerosol saline
Dunn and associates ⁴	27, F	No	> 14	20/60	20/60	Central	3.0	Unknown
Kent and associates ⁵	32, M	Yes	Infected†	20/80	20/25	Peripheral	1.5	Unknown
Kent and associates ⁵	23, M	Yes	Infected†	20/80	Pinhole vision, NA	Central	2.2	Unknown
Glastonbury and Crompton ⁶	24, NA	NA	NA	LP	20/30	Central	NA	Unknown

*NA indicates not available; CF indicates counting fingers; and LP indicates light perception.

†The infection occurred before the first lens was discarded.

complications secondary to hypoxic stress, similar to those associated with conventional soft contact lenses.

Soft contact lenses can be categorized into three groups: new lenses; worn, coated lenses; and worn lenses with large surface deposits ($\geq 150 \mu\text{m}$). *Pseudomonas aeruginosa* has been shown to adhere to new soft contact lenses when these lenses are exposed to bacteria in vitro.¹⁰ When the new lenses are worn for one or two weeks, they rapidly become coated with various tear components, especially lysozyme.¹¹ *Pseudomonas aeruginosa* can adhere to these coated lenses. *Pseudomonas aeruginosa* also adheres preferentially to large surface deposits ($\geq 150 \mu\text{m}$).¹² In disposable soft contact lenses, only the formation of large surface deposits has been eliminated.¹¹ Hence, only a part of the potential cause of infection has been eliminated. Bacteria can still adhere to new and worn, coated disposable soft contact lenses, and corneal ulceration can result. Two of the patients previously described⁵ had received new disposable soft contact lenses for the first time and developed *P. aeruginosa* corneal ulcerations within approximately two days and one day, respectively (Table). These two patients had not even removed their new lenses when the corneal infection developed. One patient from Denmark⁶ was vacationing in Australia and had her disposable soft contact lenses

mailed to her from Denmark every two weeks (Table). She developed a *P. aeruginosa* corneal ulcer while she was on vacation. In one patient,³ *P. aeruginosa* was cultured from a supposedly sterile aerosol saline solution.

In addition to cases of bacterial corneal infection, Ficker and associates⁷ described a 20-year-old woman with *Acanthamoeba* keratitis who had worn new disposable soft contact lenses for six days.

It is thus evident that, contrary to earlier predictions, disposable soft contact lenses appear not to be entirely safe with regard to infectious keratitis and corneal ulceration.

Disposable soft contact lenses have added a new dimension to contact lens use by providing convenience to the wearers, eliminating the conventional lens case as a potential source of contamination of lenses with bacteria or *Acanthamoeba*, and possibly avoiding the formation of large surface deposits ($\geq 150 \mu\text{m}$). Disposable soft contact lenses, however, can cause significant vision-threatening corneal ulceration. It is important to select individuals for disposable soft contact lens wear carefully and to instruct them about proper lens use. Preferably, these lenses should be worn on a daily-wear basis rather than for one week, and they should be discarded after two weeks of wear.

At present, one can answer the question "How safe are disposable soft contact lenses?"

by stating that these lenses certainly do not provide the solution to all problems related to conventional wear of soft contact lenses. Hence, continued caution must be exercised by all eye care specialists who dispense disposable soft contact lenses.

Reprint requests to Thomas John, M.D., Visual Sciences Center, University of Chicago, 939 E. 57th St., Chicago, IL 60637.

References

1. Killinsworth, D. W., and Stern, G.: *Pseudomonas* keratitis associated with the use of disposable soft contact lenses. *Arch. Ophthalmol.* 107:795, 1989.
2. Kershner, R. M.: Infectious corneal ulcer with overextended wearing of disposable contact lenses. *JAMA* 261:3549, 1989.
3. Rabinowitz, S. M., and Pflugfelder, S. C.: Disposable extended-wear contact lens-related keratitis. *Arch. Ophthalmol.* 107:1121, 1989.
4. Dunn, J. P., Jr., Mondino, B. J., Weissman, B. A., Donzis, P. B., and Kikkawa, D. O.: Corneal ulcers associated with disposable hydrogel contact lenses. *Am. J. Ophthalmol.* 108:113, 1989.
5. Kent, H. D., Sanders, R. J., Arentsen, J. J., Cohen, E. J., and Laibson, P. R.: *Pseudomonas* corneal ulcer associated with disposable soft contact lenses. *CLAO J.* 15:264, 1989.
6. Glastonbury, J., and Crompton, J. L.: *Pseudomonas aeruginosa* corneal infection associated with disposable contact lens use. *Aust. N.Z. J. Ophthalmol.* 17:451, 1989.
7. Ficker, L., Hunter, P., Seal, D., and Wright, P.: *Acanthamoeba* keratitis occurring with disposable contact lens wear. *Am. J. Ophthalmol.* 108:453, 1989.
8. Schwartz, C. A.: Contact lenses in the '90s. Fitting for lifestyles. *Cont. Lens Forum* 15:17, 1990.
9. Weissman, B. A., Schwartz, S. D., Gottschalk-Katsev, N., and Lee, D. A.: Oxygen permeability of disposable soft contact lenses. *Am. J. Ophthalmol.* 110:269, 1990.
10. Duran, J. A., Refojo, M. F., Gipson, I. K., and Kenyon, K. R.: *Pseudomonas* attachment to new hydrogel contact lenses. *Arch. Ophthalmol.* 105:105, 1987.
11. Davis, H., John, T., and Zeiske, J. D.: Disposable extended-wear soft contact lenses. Scanning electron microscopy and electrophoretic evaluations. ARVO abstracts. Supplement to Invest. Ophthalmol. Vis. Sci. Philadelphia, J. B. Lippincott, 1989, p. 257.
12. Aswad, M. I., John, T., Barza, M., Kenyon, K. R., and Baum, J.: Bacterial adherence to extended wear soft contact lenses. *Ophthalmology* 97:296, 1990.

LETTERS TO THE JOURNAL

Acute Dacryocystitis After Punctal Occlusion for Keratoconjunctivitis Sicca

Herbert J. Glatt, M.D.

Section of Ophthalmology, Department of Surgery, University of Tennessee Medical Center at Knoxville, and Ophthalmology Service, Department of Surgery, East Tennessee Baptist Hospital.

Inquiries to Herbert J. Glatt, M.D., University Eye Surgeons, 1928 Alcoa Highway, Knoxville, TN 37920.

A 76-year-old woman with severe keratoconjunctivitis sicca unresponsive to topical lubricants was treated with permanent occlusion of all four puncta by another physician. Three weeks later, the patient's dry eye symptoms and superficial punctate keratopathy had resolved.

Eleven weeks after punctal occlusion, the patient had left-sided pain, redness, and swelling of the medial canthal area, adjacent eyelids, and conjunctiva. The patient was treated with oral dicloxacillin and topical erythromycin.

I first examined the patient one month later. Although her symptoms had improved with antibiotic therapy, she still was in pain. On examination, a 9 × 7-mm mass was palpable in the region of the left lacrimal sac. Mild tenderness was noted. All four puncta were occluded. Pressure on the lacrimal sac mass produced no reflux of pus through the previously occluded puncta.

Three weeks later, a dacryocystorhinostomy was performed. The lacrimal sac was dilated and contained pus. Biopsy of the posterior lacrimal sac flap disclosed chronic inflammation. A small punctal dilator could be passed through

the previously occluded lower punctum into the lower canaliculus. A Bowman probe could then be passed through the lower canaliculus into the lacrimal sac. No resistance was noted at the common canaliculus. Seven weeks after the operation, the patient had no pain, and no mass was palpable in the region of the lacrimal sac. Four months after the operation, the patient continued to do well.

Acute dacryocystitis generally occurs in patients with nasolacrimal duct obstruction and chronic dacryocystitis who develop sufficient inflammatory swelling of the wall of the lacrimal sac to occlude the common canaliculus secondarily.¹ The lacrimal outflow tract is then blocked in two places, and the infectious contents of the lacrimal sac are confined within a closed space. Inflammatory exudate and cells then distend the sac, which causes the severe pain and contiguous inflammation characteristic of acute dacryocystitis. My patient presumably had preexisting asymptomatic nasolacrimal duct obstruction. Iatrogenic occlusion of the upper and lower puncta created a complete proximal block of the lacrimal outflow tract, which isolated the nonsterile contents of the lacrimal sac from any drainage outlet. The development of acute dacryocystitis 11 weeks after punctal occlusion suggests a causal relationship, although this cannot be stated with absolute certainty.

Superficial punctate keratopathy was initially noted in this patient despite the preexisting block at the level of the nasolacrimal duct and was eliminated by creation of a more proximal block at the level of the puncta. Presumably, the block of the nasolacrimal duct caused fluid

THE JOURNAL welcomes letters that describe unusual clinical or pathologic findings, experimental results, and new instruments or techniques. The title and the names of all authors appear in the Table of Contents and are retrievable through the Index Medicus and other standard indexing services. Letters must not duplicate data previously published or submitted for publication. Each letter must be accompanied by a signed disclosure statement and copyright transfer agreement published in each issue of THE JOURNAL.

Letters must be typewritten, double-spaced, on 8 1/2 × 11-inch bond paper with 1 1/2-inch margins on all four sides. (See Instructions to Authors.) An original and **two** copies of the typescript and figures must be sent. The letters should not exceed 500 words of text. A maximum of two black-and-white figures may be used; they should be cropped to a width of 3 inches (one column). Color figures cannot be used. References should be limited to five.

Letters may be referred to outside editorial referees for evaluation or may be reviewed by members of the Editorial Board. All letters are published promptly after acceptance. Authors do not receive galley proofs but if the editorial changes are extensive, the corrected typescript is submitted to them for approval.

These instructions markedly limit the opportunity for an extended discussion or review. Therefore, THE JOURNAL does not publish correspondence concerning previously published letters.

to accumulate in the lacrimal sac but did not result in significant moistening of the ocular surface.

The presence of nasolacrimal duct obstruction in a patient with dry eyes may not be obvious. Epiphora may not be present if a decrease in tear outflow is balanced by a decrease in tear production. Patients with nasolacrimal duct obstruction may remain uninfected or develop mild chronic dacryocystitis that causes minimal symptoms. Dry eyes can be associated with mucoid discharge and mild epiphora.

Before performing punctal occlusion for keratoconjunctivitis sicca, assessment of the lacrimal outflow tract is warranted. A directed history, palpation of the lacrimal sac, and canalicular irrigation may disclose evidence of nasolacrimal duct obstruction. If asymptomatic nasolacrimal duct obstruction is detected in a patient with keratoconjunctivitis sicca who is a candidate for punctal occlusion, prophylactic dacryocystorhinostomy may be considered to prevent precipitation of acute dacryocystitis. Even if prophylactic dacryocystorhinostomy is not performed, assessment of the lacrimal outflow tract before punctal occlusion will simplify subsequent evaluation of a mass in the region of the lacrimal sac.

Reference

1. Meyer, D. R., and Linberg, J. V.: Acute dacryocystitis. In Linberg, J. V. (ed.): *Oculoplastic and Orbital Emergencies*. Norwalk, Connecticut, Appleton and Lange, 1990, pp. 29-43.

Macular Edema in Acquired Immunodeficiency Syndrome-Related Microvasculopathy

Alan G. Palestine, M.D.,
and Benjamin Frishberg, M.D.

Inquiries to Alan G. Palestine, M.D., 1145 19th St. N.W., Ste. 607, Washington, DC 20036.

The most common ocular manifestation of the acquired immunodeficiency syndrome is the development of a noninfectious retinopathy consisting of cotton-wool spots, small retinal hemorrhages, and microvascular abnormali-

ties, such as microaneurysms, telangiectasia, and capillary loss.¹⁻³ The observed characteristics of the retinal abnormalities do not differ significantly from those present in diabetes mellitus, hypertension, and collagen vascular diseases. These clinical findings result from a microvasculopathy that is pathologically similar to diabetes mellitus.^{2,4} This background retinopathy has been observed in 30% to 53% of patients with AIDS.^{1,3,5} Microvascular fluorescein angiographic abnormalities were reported in all 13 patients in the study of Newsome and associates.⁴ The more severe manifestations of microvascular retinal disease, however, such as macular edema or proliferative retinopathy, have not been observed in patients with AIDS. The fundamental cause for the appearance of microvascular retinal disease in patients with AIDS is still unclear, but deposition of circulating immune complexes has been implicated.² These findings are more frequently observed as patients develop increasing immunosuppression from the human immunodeficiency virus infection. We treated a patient who developed symptomatic macular edema related to microvascular retinal disease.

A 59-year-old woman was examined for a recent decrease in vision in the left eye. Visual acuity was R.E.: 20/30 and L.E.: counting fingers. Examination disclosed a small patch of cytomegalovirus retinitis in the right eye nasal to the optic disk with multiple cotton-wool spots in the posterior pole. The left eye had



Fig. 1 (Palestine and Frishberg). Fluorescein angiogram of the right eye demonstrating microvascular retinal leakage without perifoveal telangiectasia or leakage in the presence of clinical cystoid macular edema. Visual acuity was 20/200.

extensive cytomegalovirus optic neuropathy. The patient had been HIV positive for four years and had been well until two months before her visual symptoms, when she developed a progressive weight loss, fatigue, and diarrhea followed by a progressive ataxia. A magnetic resonance imaging scan was consistent with HIV encephalitis.

The patient received a two-week regimen of 5 mg/kg of body weight of ganciclovir twice daily for induction followed by 5 mg/kg of body weight daily. She returned after the induction therapy with a marked decrease in vision in the right eye. The cytomegalovirus retinitis was inactive in both eyes, but there was extensive cystoid macular edema in the right eye with visual acuity of 20/200. Fluorescein angiography disclosed multiple foci of microvascular retinal leakage in the posterior pole without leakage near the fovea (Fig. 1). Visual-evoked potential testing demonstrated no abnormalities in the right eye. Light focal argon green laser photocoagulation was applied to the microvascular abnormalities in the right eye. Two weeks later visual acuity improved to 20/70 with the appearance of new lipid exudates in the macula. After three additional weeks, visual acuity improved to 20/50 with the development of a prominent macular star as the macular edema resolved totally (Fig. 2). Visual acuity remained stable at 20/40 one month later.

The development of a macular star is consistent with macular edema induced by a microvasculopathy. Lipid exudates associated with macular edema are common in diseases such as diabetes mellitus but are rarely observed in retinal inflammations despite the extensive macular capillary leakage. Additionally, diabetic macular edema responds to laser photocoagulation, whereas the macular edema of retinal inflammation does not respond. The development of AIDS-related macular edema is unusual, but, as in diabetes mellitus, this may be related to the length of time that the underlying disease is present. If survival for patients with AIDS increases significantly, this may become a more frequently observed and potentially treatable cause of visual loss.

References

1. Palestine, A. G., Rodrigues, M. M., Macher, A. M., Chan, C.-C., Lane, H. C., Fauci, A. S., Masur, H., Longo, D., Reichert, C. M., Steis, R., Rook, A. H.,

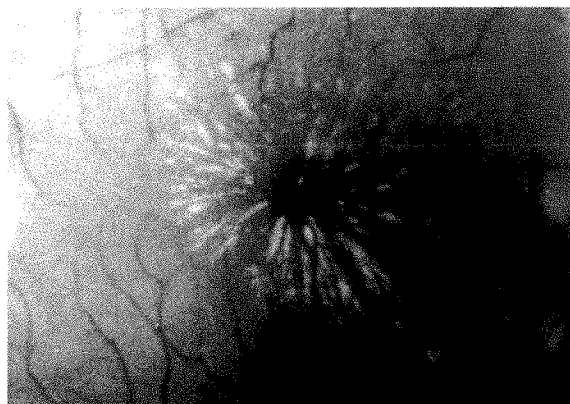


Fig. 2 (Palestine and Frishberg). The right eye five weeks after laser photocoagulation demonstrating the development of a macular star with the disappearance of clinical macular edema. Visual acuity was 20/50 +2.

and Nussenblatt, R. B.: Ophthalmic involvement in acquired immunodeficiency syndrome. *Ophthalmology* 91:1092, 1984.

2. Pepose, J. S., Holland, G. N., Nestor, N. S., Cochran, A. J., and Foos, R. Y.: Acquired immunodeficiency syndrome. Pathogenic mechanisms of ocular disease. *Ophthalmology* 92:472, 1985.

3. Holland, G. N., Pepose, J. S., Pettit, T. H., Gottlieb, M. S., Yee, R. D., and Foos, R. Y.: Acquired immune deficiency syndrome. Ocular manifestations. *Ophthalmology* 90:859, 1983.

4. Newsome, D. A., Green, W. R., Miller, E. D., Kiessling, L. A., Morgan, B., Jabs, D. A., and Polk, B. F.: Microvascular aspects of acquired immune deficiency syndrome retinopathy. *Am. J. Ophthalmol.* 98:590, 1984.

5. Freeman, W. R., Lerner, C. W., Mines, J. A., Lash, R. S., Nadel, A. J., Starr, M. B., and Tapper, M. L.: A prospective study of the ophthalmologic findings in the acquired immune deficiency syndrome. *Am. J. Ophthalmol.* 97:133, 1984.

Transient Cranial Nerve Palsies After Cavernous Sinus Fistula Embolization

**Felix N. Sabates, Jr., M.D.,
Fong Tsai, M.D.,
Nelson R. Sabates, M.D.,
and Bryan Blitstein, M.S.**

Departments of Ophthalmology (F.N.S., N.R.S.) and Neuroradiology (F.T., B.B.), University of Missouri-Kansas City.

Inquiries to Felix N. Sabates, Jr., M.D., Department of Ophthalmology, University of Missouri, Kansas City, KS 64108.

Treatment of carotid-cavernous sinus fistulas by balloon embolization has resulted in low morbidity and mortality.¹⁻³ The development of transient and permanent cranial nerve palsies after successful embolization of carotid-cavernous sinus fistulas, however, has been reported to be as high as 67% and 33%, respectively.^{1,2} We treated a patient who underwent balloon embolization of a direct carotid-cavernous sinus fistula and developed transient multiple cranial nerve palsies.

A 21-year-old man had a continual rushing noise, heard mostly on the left side of his head, and stabbing pain in the left eye. Approximately six months previously, the patient had sustained direct trauma to the left side of his face. Initially, he had a gradual decrease and eventual loss of vision during a one-month period and a gradual worsening of the constant rushing noise. Visual acuity was 20/20 in the right eye, and results of external and fundus examinations were normal. Visual acuity of the affected left eye was 20/200, and external examination disclosed a palpable thrill over the left orbit. The pupil was 6 mm and sluggishly reactive with a marked afferent pupillary defect. Extraocular movements were full except on upgaze. A 20-diopter exotropia was noted. The left eye was proptotic with a Hertel exophthalmometry reading of 24, compared to 16 in the right eye. The scleral vessels were engorged (Fig. 1). Intraocular pressure varied with the supraorbital pulsations between 24 and 32 mm Hg. Ophthalmoscopy showed a pale disk with slightly increased tortuosity of fundus vessels as com-



Fig. 1 (Sabates and associates). Engorged scleral vessels in the left eye.

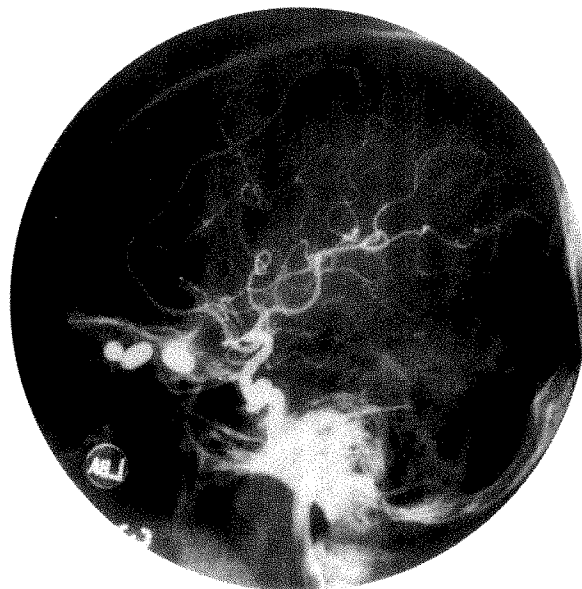


Fig. 2 (Sabates and associates). Arteriogram of left internal carotid artery after balloon embolization. Note closure of the fistula.

pared to the vessels of the unaffected eye. A computed tomographic scan disclosed a dilated superior ophthalmic vein and a tripod fracture of the orbit. Arteriography confirmed the diagnosis of carotid-cavernous sinus fistula. Balloon embolizations closed the fistula successfully on the fourth attempt (Fig. 2).

Nine days postoperatively, the patient developed multiple cranial nerve palsies, including the oculomotor nerve, the trochlear nerve, the upper branch of the olfactory nerve, and the abducent nerve. Repeat scans disclosed a generalized enlargement of the previously embolized balloons. We speculated that imbibition of fluid into the balloon enlarged its original size and caused compression of the cranial nerves located in the venous sinus. The balloon contains contrast media that can often have twice the serum osmolality.

We attempted to change the osmotic gradient and decrease the size of the balloon. Normal saline (2 l) and furosemide (80 mg) were given initially to increase the serum osmolality. The patient was also given 200 mg of carbamazepine orally three times a day. The urine and serum osmolalities and the blood urea nitrogen and creatinine levels were monitored closely. The initial serum osmolality was 274 mOsm upon admission with a urine osmolality of 431 mOsm. After three days of constant diuresis, a serum osmolality of 312 mOsm was attained and coincided with resolution of all the cranial

nerve palsies. Repeat scans showed a reduction in size of the previously enlarged balloon to a size smaller than it was originally. We believe that our attempts at hemoconcentration of the serum was responsible for alleviating the pain and cranial nerve palsies rapidly, but we cannot rule out the possible therapeutic involvement of carbamazepine.

References

1. Tsai, F. Y., Hieshima, G. B., Mehringer, C. M., Grinnell, V., and Pribam, H. W.: Delayed effects in the treatment of carotid-cavernous fistulas. *AJNR* 4:357, 1983.
 2. Keltner, J. L., Satterfield, D., and Dublin, A. B.: Dural and carotid cavernous sinus fistulas. *Ophthalmology* 12:1585, 1987.
 3. Halbach, V. V., Higashida, R. T., and Hieshima, G. B.: Interventional neuroradiology. *AJR* 153:467, 1989.
-

Contralateral Cavernous Sinus Syndrome After Retrobulbar Anesthetic Injection

**P. Andrew Pearson, M.D.,
Kerry D. Solomon, M.D.,
Thomas J. Smith, M.D.,
and Avrom D. Epstein, M.D.**

Department of Ophthalmology, University of Kentucky.

Inquiries to P. Andrew Pearson, M.D., Department of Ophthalmology, University of Kentucky, 801 Rose St., Lexington, KY 40536-0223.

Complications of retrobulbar injections most commonly result from mechanical injury to the eye. Nervous system complications include generalized seizures and obtundation, presumably from intrathecal injection. Oculomotor weakness in the contralateral eye is uncommon.¹⁻³

A 62-year-old man was admitted for planned left extracapsular cataract extraction under local anesthesia. Preoperative ocular examination showed bilateral cataracts and a 15-diopter alternating exotropia. Versions were full, and there was no relative afferent pupillary defect. The anesthetic was a 50:50 mixture of 2% lidocaine and 0.5% bupivacaine hydrochloride with 150 USP units/10 ml of hyaluronidase.

After an uncomplicated modified Van Lint injection of 5 ml, a 4-ml retrobulbar injection was given with a sharp, 3.2-cm, 25-gauge needle. The injection was given through the lower eyelid at the junction of the lateral one third and medial two thirds with the patient looking straight ahead. When the tip of the needle was beyond the rear of the globe, it was directed superiorly to a total depth of approximately 2.5 cm. There was no blood return on aspiration before injection. Approximately ten to 15 seconds after the injection the patient had rigors and shivering that he could not control. He remained alert with no respiratory depression. His systolic blood pressure increased from 150 to 195 mm Hg, and he was treated with 5 mg of intravenous labetalol hydrochloride. The rigors resolved in approximately two minutes. After the injection there was incomplete akinesia of the left (ipsilateral) eye, with some motility in all fields of gaze. Examination of the other eye demonstrated dysfunction of the oculomotor, trochlear, ophthalmic, maxillary, and abducent nerves. Snellen visual acuity was not measured; however, the patient reported no decrease in vision. As pupil function returned, there was no relative afferent pupillary defect. All deficits resolved within one hour.

We believe this case represents a contralateral cavernous sinus syndrome consequent to retrobulbar anesthesia. This patient's syndrome may have resulted from injection of anesthetic into an orbital vein, which then passed to the contralateral cavernous sinus by way of the intercavernous sinus that connects the two cavernous sinuses. The promptness of the patient's shivering suggests intravascular injection and systemic distribution of the anesthetic. Simultaneous deficits in the contralateral oculomotor, trochlear, trigeminal, and abducent nerves strongly suggest a disturbance in the cavernous sinus. Previous reports of contralateral motility deficits implicated unintended injection into the subdural^{1,2} or subarachnoid space.³ A subarachnoid injection sufficient to block the contralateral eye should be accompanied by other nervous system abnormalities. Similarly, subdural injection of anesthetic should not cause shivering. Other reports of contralateral ocular motor weakness without blindness after retrobulbar anesthesia might be similarly explained. Despite the absence of blood reflux with aspiration before injection, unintended intravascular administration is still possible. Cavernous sinus injection should be included in the list of potential complications

of retrobulbar injection. Only supportive care and observation were required in this case.

References

1. Antoszyk, A. N., and Buckley, E. G.: Contralateral decreased visual acuity and extraocular muscle palsies following retrobulbar anesthesia. *Ophthalmology* 93:462, 1986.
2. Reed, J. W., Macmillan, A. S., and Lazenby, G. W.: Transient neurologic complication of positive contrast orbitography. *Arch. Ophthalmol.* 81:508, 1969.
3. Brookshire, G. L., Gleitsmann, K. Y., and Schenk, E. C.: Life-threatening complication of retrobulbar block. *Ophthalmology* 93:1476, 1986.

Retinopathy in Human Vitamin E Deficiency

Adam S. Berger, M.D.,
Lawrence Tychsens, M.D.,
and Jerry L. Rosenblum, M.D.

Department of Ophthalmology and Visual Sciences, Children's Hospital Eye Center (A.S.B., L.T.), and Division of Gastroenterology and Nutrition, Department of Pediatrics (J.L.R.), Washington University School of Medicine.

Inquiries to Lawrence Tychsens, M.D., Room 2s89, St. Louis Children's Hospital, Washington University Medical Center, 400 S. Kingshighway, St. Louis, MO 63110.

Combined deficiency of vitamins A and E is known to cause nyctalopia and retinal degeneration in humans.¹ The pathologic effect of a deficiency in vitamin E alone, however, is unclear. We treated a patient with avitaminosis E of 18 years' duration. The patient developed progressive nyctalopia and pigmentary retinopathy. Serum vitamin A levels for the last 15 of those 18 years were, with one exception, within the normal range.

A 28-year-old man with an autosomal recessive form of intrahepatic cholestasis, characterized by malabsorption of fat-soluble vitamins, had been followed up in the pediatric gastroenterology unit for 18 years. In the 18th year of follow-up, the patient developed a neurologic syndrome consistent with vitamin E deficiency after being lost to follow-up for eight years.² He was referred for ophthalmic consultation because of a recent decrease in vision. Best-corrected visual acuity was R.E.: 20/30 and L.E.: 20/40. Goldmann visual fields were constricted and depressed. Color vision testing disclosed a generalized dyschromatopsia. The dark adaptation threshold was increased by 2.5 log units in each eye. An electroretinogram showed severely attenuated signals on photopic and scotopic testing in each eye, with maximal voltage of 35 μ V (normal, greater than 350 μ V). Ophthalmoscopy disclosed widespread retinal pigment epithelium dropout and pigment clumping (Fig. 1). There was diffuse loss of nerve fiber layer accompanied by mild disk pallor.

The patient had bilateral blepharoptosis, facial diplegia, coarse head titubation, and a right

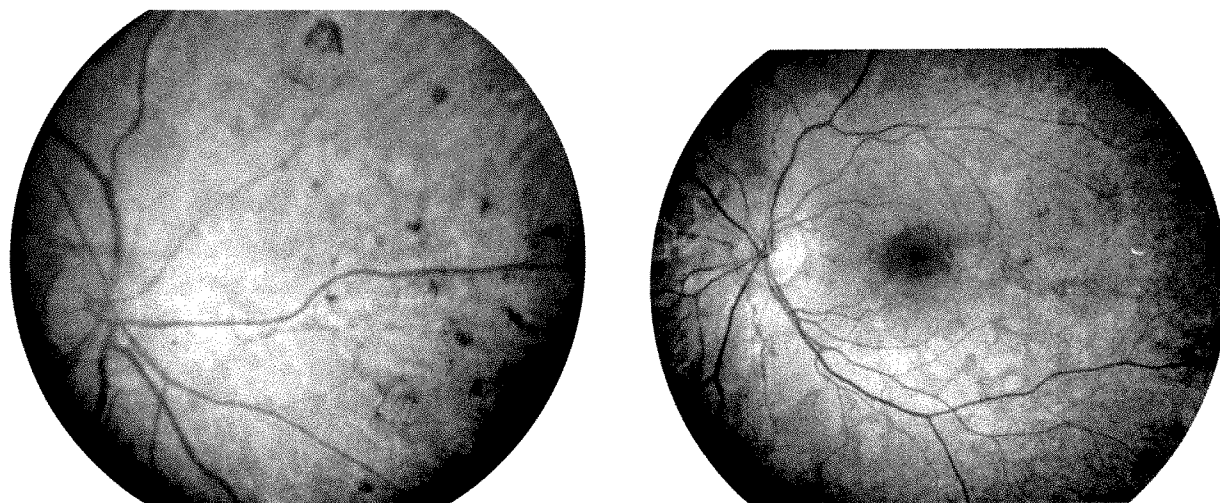


Fig. 1 (Berger, Tychsens, and Rosenblum). Widespread depigmentation, pigment clumping (left), narrowing of retinal arterioles, and scalloped foci of pigment dropout within the vascular arcades and loss of the foveal reflex (right).

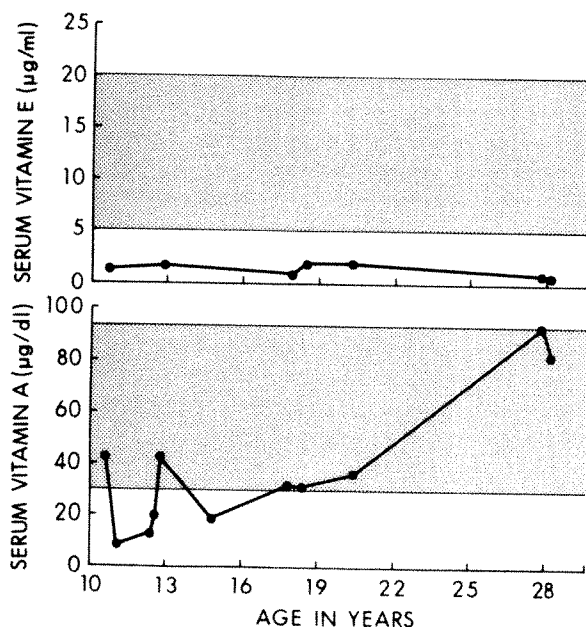


Fig. 2 (Berger, Tychsén, and Rosenblum). Serum vitamin E and A levels during an 18-year period. The shaded area represents the normal range.

head tilt. Ocular motility examination showed bilateral reverse internuclear ophthalmoplegia, bilateral abducent nerve palsies, and skew deviation. These neurologic and ocular motor features have been described in previous reports of patients with avitaminosis E.^{2,3} Additionally, our patient had pupillary light-near dissociation.

The patient's serum vitamin E and A levels were measured for 18 years (Fig. 2). The patient was given d-alpha tocopheryl polyethylene glycol-1,000-succinate, an experimental, water-miscible, oral form of vitamin E. Despite normal vitamin E levels for one year, there was no improvement in the ophthalmoscopic appearance, visual acuity, dark adaptation threshold, or electroretinogram.

The findings in our patient demonstrate that chronic vitamin E deficiency, during a period of 18 years, can cause progressive pigmentary retinopathy in the absence of chronic vitamin A deficiency. Cogan and associates¹ documented photoreceptor degeneration by postmortem ocular histopathologic examination in a patient who had combined vitamin A and E deficiency. Alvarez and associates⁴ reported pigmentary retinopathy in a cohort of patients with low vitamin E levels. They documented a single serum vitamin A level and for this reason could

not exclude concomitant vitamin A deficiency as a contributing factor.

Vitamin A is necessary for production of rhodopsin. Vitamin E is known to be concentrated in photoreceptor outer segments and is thought to protect photoreceptor membranes from oxidative damage. Vitamin E deprivation in animals causes marked disruption of outer segments and an increase in lipofuscin granules in the retinal pigment epithelium.⁵ These changes are attributed to peroxidation of photoreceptor lipoproteins composed of unsaturated fatty acids. The findings in our patient imply that deficiency of vitamin E is the major factor responsible for the ophthalmoscopic and electrophysiologic abnormalities previously reported in humans who have combined deficiency of vitamins A and E.

References

1. Cogan, D. G., Rodriguez, M., Chu, F. C., and Schaefer, E. J.: Ocular abnormalities in abetalipoproteinemia. A clinicopathologic correlation. *Ophthalmology* 91:991, 1984.
2. Rosenblum, J. L., Keating, J. P., Prensky, A. L., and Nelson, J. S.: A progressive neurologic syndrome in children with chronic liver disease. *N. Engl. J. Med.* 304:503, 1981.
3. Yee, R. D., Cogan, D. G., and Zee, D. S.: Ophthalmoplegia and dissociated nystagmus in abetalipoproteinemia. *Arch. Ophthalmol.* 94:571, 1976.
4. Alvarez, F., Landrieu, P., Laget, P., Lemonnier, F., Odière, M., and Alagille, D.: Nervous and ocular disorders in children with cholestasis and vitamin A and E deficiencies. *Hepatology* 3:410, 1983.
5. Robison, W. G., Kuwabara, T., and Bieri, J. G.: Vitamin E deficiency and the retina. Photoreceptor and pigment epithelial changes. *Invest. Ophthalmol. Vis. Sci.* 18:683, 1979.

Keratoconus and Congenital Hip Dysplasia

Paolo Nucci, M.D.,
and Rosario Brancato, M.D.

Clinica Oculistica dell'Università di Milano, Istituto Scientifico H. S. Raffaele.

Inquiries to Paolo Nucci, M.D., Clinica Oculistica dell'Università di Milano, Ospedale S. Raffaele, via Olgettina 60, 20132 Milano, Italy.

Congenital hip dysplasia denotes a delayed or defective development of the hip joint and its

associated structure. If untreated, the condition heals, persists as a subluxation, or progresses to a frank dislocation. Genetic, ethnic, and uterine factors play a role in its pathogenesis. Congenital hip dysplasia occurs once in every 110 births, with a female sex predilection of approximately 5 to 1. A family history of the condition is noted in 12% to 33% of patients.¹

Two sisters, aged 9 and 12 years, were examined by one of us (P.N.) for blurred vision and photophobia. They were the only children of healthy, consanguineous parents whose mothers were sisters.

Both girls were delivered vaginally at term and had Apgar scores of 9/9. Both girls had bilateral congenital hip dysplasia, related to an acetabular dysplasia, diagnosed by ultrasonography at age 6 months in the older sister and at age 3 months in the younger sister. There was no family history of hip dysplasia.

The younger sister had best-corrected visual acuity of 20/20 in each eye with refraction of R.E.: +1.00 +1.25 \times 30 and L.E.: -1.00 -1.25 \times 15. The older sister had best-corrected visual acuity of R.E.: 20/40 and L.E.: 20/30 with refraction of R.E.: -2.00 -3.25 \times 40 and L.E.: -1.75 -2.75 \times 35. Keratometric readings disclosed distorted mires in each girl. Biomicroscopic examination disclosed a cone-shaped ectasia of the cornea in each girl. Vogt's striae were noted in the deep stroma and Descemet's membrane of the older girl. The endothelial cell count was within normal limits (2,890 \pm 121 cells/mm² in the younger sister and 2,914 \pm 321 cells/mm² in the older sister).² The appearance of the corneas was consistent with bilateral keratoconus. No evidence of other corneal dystrophies was noted. The ophthalmic history was unremarkable for atopic diseases, ocular trauma, eye rubbing, or hard contact lens use.

Keratoconus usually becomes manifest during adolescence. Most cases of keratoconus are sporadic, but it is sometimes familial. Kennedy, Bourne, and Dyer³ described keratoconus occurring in less than 6% of the blood relatives of an affected proband. Greenfield and associates⁴ reported a familial occurrence of keratoconus and osteogenesis imperfecta and hypothesized an autosomal recessive pattern of inheritance. Several systemic tissue disorders are reported in association with keratoconus, including Marfan's syndrome and Ehlers-Danlos syndrome.³ Reports of consanguinity have been cited as evidence of a recessive mode of inheritance. Wynne-Davies⁵ suggested a multiple gene heredity defect in congenital hip dysplasia with acetabular dysplasia, especially when environmental factors had not played a role.

The incidence of keratoconus ranges from 50 to 200 per 100,000 live births, whereas congenital hip dysplasia occurs once in 110 live births. Therefore, congenital hip dysplasia and keratoconus is an association of two independent events whose incidence ranges from 4 to 18 per 1,000,000 live births. Mathematically, the probability that this association occurs twice by chance is extremely low. The early development of keratoconus and the consanguinity of the parents support the hypothesis that this is most likely an autosomal recessive association.

References

1. Coleman, S. S.: Diagnosis of congenital dysplasia of the hip in the newborn infant. *Clin. Orthop.* 247:3, 1989.
 2. Nucci, P., Brancato, R., Mets, M. B., and Shevell, S. K.: Normal endothelial cell density range in childhood. *Arch. Ophthalmol.* 108:247, 1990.
 3. Kennedy, R. H., Bourne, W. M., and Dyer, J. A.: A 48-year clinical and epidemiologic study of keratoconus. *Am. J. Ophthalmol.* 101:267, 1986.
 4. Greenfield, G., Romano, A., Stein, R., and Goodman, R. M.: Blue sclera and keratoconus. Key features of a distinct heritable disorder of connective tissue. *Clin. Genet.* 4:8, 1973.
 5. Wynne-Davies, R.: Acetabular dysplasia and familial joint laxity. Two etiological factors in congenital dislocation of the hip. A review of 589 patients and their families. *J. Bone Joint Surg. [Br.]* 52:704, 1970.
-

Flexible Iris Retractor

**Eugene de Juan, Jr., M.D.,
and Dyson Hickingbotham**

Department of Ophthalmology, Duke University Eye Center. Duke University will receive royalties based on the sale of the iris retractors; however, the authors will receive no direct compensation.

Inquiries to Eugene de Juan, Jr., M.D., Duke University Eye Center, Box 3802, Durham, NC 27710.

Inadequate pupillary dilation can occur during ocular surgery or as a result of scarring near the pupillary margin from many causes. A variety of methods have been developed to correct this problem, including iris sphincterotomy, several suture techniques,¹⁻³ metal iris retractors placed either through the pars plana or the corneoscleral limbus,^{4,5} and pharmacologic methods. None of these methods, however, are sufficiently delicate for use in the phakic eye when the lens is to be retained. The inflexible

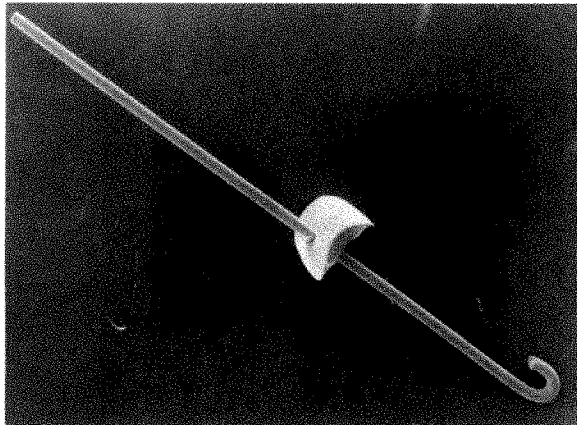


Fig. 1 (de Juan and Hickingbotham). Scanning electron micrograph of flexible iris retractor showing Silastic sleeve and hook.

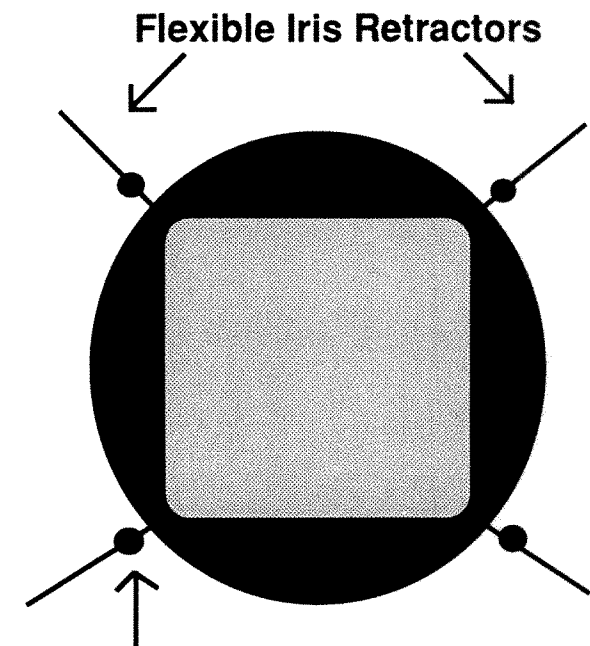
metal iris retractor can damage the anterior lens capsule, particularly when manipulation of the globe causes the end of the retractor to push against the delicate intraocular tissues. To overcome these limitations, we developed and tested a new iris retractor with a flexible nylon hook and a Silastic sleeve. The retractor is 6.0 mm in length and has a 1.0-mm hook at the end. The small Silastic disk holds the retractor in place (Fig. 1).

Since both the tip and the shaft of the retractor are flexible, damage to ocular structures is minimal, particularly to the anterior capsule in phakic eyes. Placement of the retractor is facilitated by a specially developed 0.5-mm spatula-shaped knife, which makes a self-sealing limbal incision. The flexible iris retractors are compatible with sutured-on contact lens rings used during vitreous surgery and can be cut to any length to avoid interference with anterior segment manipulations (Fig. 2).

The flexible iris retractor is placed and held by a small needle holder for secure manipulation. The iris retractor is grasped near the hooked end to facilitate insertion through the corneal incision. Once the retractor has been inserted into the anterior chamber, the needle holder is then turned so that the retractor can hook the edge of the iris and pull it toward the entry site. The Silastic collar can then be adjusted to the appropriate length and tension.

Removal of the retractor is accomplished by reversing the steps. When the hooked portion of the retractor comes close to the self-sealing corneal incision, it will bend and slip out. It does not require specific orientation as metal hooks do.

We have had few problems related to the use of the flexible iris retractors. They are strong



Silastic sleeves

Fig. 2 (de Juan and Hickingbotham). Pupillary dilation facilitated by flexible iris retractor.

enough to break even firmly adherent synechiae yet flexible enough to prevent damage to the anterior capsule in phakic eyes. The anterior chamber did flatten in one eye at the end of a fluid-gas exchange because of leakage of aqueous fluid around the retractor. The chamber was reformed by injecting balanced salt solution, and the lens capsule was not damaged. This leakage can be minimized by using the knife and by using low infusion pressures during the fluid-gas exchange.

References

1. Eckardt, C.: Pupillary stretching. A new procedure in vitreous surgery. *Retina* 5:235, 1985.
2. Madeira, D., and Stern, W. H.: Iris suture hook for pupillary dilation in vitreoretinal surgery. *Am. J. Ophthalmol.* 106:743, 1988.
3. Zivojnovic, R.: *Silicone Oil in Vitreoretinal Surgery*. Dordrecht, The Netherlands, Martinus Nijhoff Publishers, 1987, p. 126.
4. McCuen, B., Hickingbotham, D., Tsai, M., and de Juan, E., Jr.: Temporary iris fixation with a micro-iris retractor. *Arch. Ophthalmol.* 107:925, 1989.
5. Fuller, D. G., and Wilson, D. L.: Translimbal iris hook for pupillary dilation during vitreous surgery. *Am. J. Ophthalmol.* 110:577, 1990.

BOOK REVIEWS

Edited by H. Stanley Thompson, M.D.

Cosmetic Blepharoplasty. By Stephen L. Bosniak. New York, Raven Press, 1990. 114 pages, index, illustrated. \$95

Reviewed by MICHAEL PATIPA
Palm Beach, Florida

Cosmetic eyelid surgery is a timely topic. There seems to be an increased level of interest in these procedures among ophthalmologists. Other specialists are beginning to do cosmetic eyelid surgery, and the patients themselves often bring up the subject.

This text is offered as a "complete guide to cosmetic eyelid surgery," but it is more of an introductory text than a complete guide. The introduction it provides is a good one.

The first chapter is thorough in its coverage of the preoperative examination of the patient. It provides many basic warnings about potential problem cases and difficult clinical situations that the cosmetic surgeon may encounter. The tables and differential diagnoses are informative. There is an interesting flowchart showing the steps the author goes through when performing eyebrow surgery and cosmetic blepharoplasty.

There are a few problems: the entire section on bipolar lipolytic diathermy appears to be in the wrong place in the book; references are not cited in the text; and reference is made to certain procedures (for example, lower eyelid retractor recession for ectropion repair) without telling the reader where to look for more information on the subject.

The chapters on adjunctive techniques in cosmetic surgery, blepharoplasty in males, and upper eyelid blepharoplasty in the Asian patient are informative. These three chapters would be valuable for any surgeon looking for another cosmetic surgeon's perspective before undertaking one of these procedures.

The chapter on diagnosis and treatment of complications of cosmetic eyelid surgery briefly discusses most of the complications encountered in clinical practice; however, it glaringly overlooks the treatment of orbital hemorrhage during or after cosmetic blepharoplasty.

This is an excellent introductory text for anyone beginning to do cosmetic surgery. It allows the reader to share in Dr. Bosniak's considerable experience with oculoplastic surgery, but as a complete guide to cosmetic eyelid surgery, it falls short.

Ptosis, ed. 4. By Michael Callahan and Crowell Beard. Birmingham, Alabama, Aesculapius Publishing, 1990. 319 pages, index, illustrated. \$125

Reviewed by JONATHAN J. DUTTON
Durham, North Carolina

In 1969, Crowell Beard published the first edition of his now classic book on blepharoptosis. Since that time and through two successive editions, this text has become a standard reference both for beginning students and seasoned surgeons. Changes in concepts of classification and improved understanding of anatomic relationships within the eyelids, however, have altered our approach to blepharoptosis surgery. The result was that the third edition of this book has been out of date for some years. This has now been corrected in the fourth edition by Michael Callahan.

The most obvious change is a larger format that is easier to read. Between the covers, the text has been markedly reorganized. Many outdated procedures have been omitted, and other rarely used operations have been grouped in one short chapter. This reorganization has eliminated the confusing array of procedures in the earlier editions, often presented without clear indications of when each was to be used. The major portion of the text covers only four standard operations, all of which have proven most predictable. These are the Fasanella-Servat procedure, levator aponeurosis advancement, levator muscle resection, and frontalis suspension. Unlike previous editions, postoperative results and complications are listed in the same chapters as their respective surgical descriptions, thus avoiding constant page-flipping. The expanded text has been supplemented with excellent new color drawings. A chapter has been added on related operations covering deformities often associated with blepharoptosis, such as epicanthal folds, dermatochalasis, and eyebrow blepharoptosis. The chapter on eyelid anatomy has been rewritten, and a number of color drawings have been added to clarify the sometimes confusing cadaver dissections that have been retained. Excellent chapters on physiology and pathology round out the volume.

It would be difficult to find much to criticize in this book. It is well organized, nicely illustrated, and clearly written. Some problems per-

sist, however, such as the confusion between the levator horns and Whitnall's ligament, which seems to have found its way into nearly every book on blepharoptosis. Perhaps the most disappointing chapter is the one on classification. Dr. Callahan correctly points out the problems with older, nonetiologic classifications and stresses the need for a mechanistic approach. Indeed, he recognizes four major categories of blepharoptosis: levator maldevelopment (myogenic), aponeurotic, neurogenic, and mechanical/apparent. Yet he goes on to propose several seemingly nondescriptive and nonetiologic groups, such as "simple levator maldevelopment" for congenital developmental dystrophic blepharoptosis. Under aponeurotic blepharoptosis are included such confusing categories as "senile ptosis," "following cataract surgery," "following local trauma," and "blepharochalasis." Such groupings add little to our understanding of origin, since all of them relate to aponeurotic redundancy or dehiscence. Rather than being types of blepharoptosis, these, among many others not listed, are actually causes of aponeurotic blepharoptosis.

Despite these few critical comments, Michael Callahan has achieved more in this new edition than just the resurrection of a classic book. In many ways it represents a new volume, one that will itself become a standard in the field of blepharoptosis surgery. Dr. Callahan's stated goal was to bring this book abreast of modern times and to make it useful to those who perform these procedures. He has achieved these goals admirably. This book should certainly be on the shelf of any surgeon who examines and treats patients with blepharoptosis.

Color Atlas of Ophthalmic Surgery. Strabismus.

By Kenneth W. Wright. Philadelphia, J. B. Lippincott, 1990. 261 pages, index, illustrated. \$125

Reviewed by RONALD V. KEECH
Iowa City, Iowa

This is the first volume in a series on ophthalmic surgery, which illustrates surgical procedures with drawings and color photographs. The intent of the book is to provide a "practical text to teach strabismus surgical technique" to the novice and as well as expand the "surgical repertoire of the experienced surgeon."

Beginning surgeons will appreciate the chap-

ters on anatomy and basic surgical technique. They will also benefit from the concise summary of surgical indications found in many of the chapters and the recommended surgical amounts for resections and recessions listed in the appendices. A note of caution to the novice: some procedures, such as the silicone expander operation used for weakening the superior oblique muscle, may be misinterpreted as a procedure preferred by most strabismus surgeons, when in reality it is an intriguing but not well-established technique.

Veteran strabismus surgeons may profit from the chapters on adjustable sutures, posterior fixation sutures, and chemodenervation (botulinum) surgery. The drawings and color photographs clearly demonstrate the techniques, and the references, while not exhaustive, are current.

The six contributors do a good job of describing and illustrating strabismus surgical techniques. As a result, this book should be valuable in training residents and fellows.

The History of Ophthalmology, vol. 9. The First and Second Half of the Nineteenth Century. By Julius Hirschberg. Translated by Frederick C. Blodi. Germany, Verlag, 1990. 332 pages, index, illustrated. \$180

Reviewed by FRANK W. NEWELL
Chicago, Illinois

After delay of a little more than two years, publication of Frederick Blodi's translation into English of Julius Hirschberg's "The History of Ophthalmology" has resumed with the appearance of volume 9, "The First and Second Half of the Nineteenth Century, United States of America, Switzerland, and Belgium."

The original of the section on the United States was published in Leipzig in 1915 as a continuation of the Graefe-Saemisch-Hess Handbuch der Gesamten Augenheilkunde under the editorial direction of Professors Saemisch and Elschnig. Blodi's translation of "Ophthalmology in the United States" omits only the dedication of the original to the Ophthalmological Society of Colorado, which was founded by Edward Jackson. Julius Hirschberg visited the United States three times and in this volume described an incident of his horse rearing while touring Yellowstone National Park with Hermann Knapp.

The History extends beyond the end of the 19th century and describes events as late as 1914.

Hirschberg concluded the United States history with the statement, "The size of the country and the number of inhabitants, the resources and the industrial richness, the intelligence and ambition of the citizens and especially the liberal institutions of the United States government make advances in civilization, including our specialty, for this country not only justified, but necessary." In some ways, we have fulfilled this hope, but more is still necessary.

The sections on Switzerland and Belgium are limited; each fills about 50 pages (the number of pages in the volume is approximately equal to the original but the new volumes are far more attractive).

The section on Switzerland is divided about equally between the University of Basel, and the cities of Zurich and Geneva. The study of ophthalmology in Belgium was initiated, as in England, by the ravages of military ophthalmia (trachoma) after Napoleon's Egyptian campaign. Hirschberg documented the founding of the *Annales d'Oculistique* by Florent Cunier in 1838. The journal's name disappeared in 1978 when it merged with the *Archives d'Ophtalmologie*, founded in 1853, to form the *Journal Français Ophtalmologie*. Hirschberg complained of the lack of representative German ophthalmologists on the Editorial Board. He described Evariste Warlomont, founder of the *Annales d'Oculistique*, who initiated the First International Congress of Ophthalmology in Brussels in 1857.

It is exciting to have both this ninth volume appear and the promise of the remaining volumes in the near future. English-speaking ophthalmologists are indebted to the scholarship of Professor Blodi.

EndNote Plus. Berkeley, Niles & Associates, 1990. Computer disk and 216-page manual, index. \$249

Reviewed by W. L. M. ALWARD
Iowa City, Iowa

EndNote Plus is a computer software package that gives physicians and scientists a way to handle the vast quantity of information ob-

tained from reading scientific literature. It is available in both IBM and Macintosh formats. I have worked only with the Macintosh version on a Mac SE-30 computer.

EndNote Plus has two purposes and fulfills both beautifully. First, it is a data base manager designed specifically for storing and retrieving references. References are easily entered into a template that has fields for authors' names, title, journal, and the like. There are also fields for abstracts and notes, each of which will hold up to 32,000 characters. Entry of data into EndNote Plus is easy and self-explanatory.

The most useful feature of the EndNote Plus data base is its ability to search for information. When asked to find a word or word fragment, it will search all fields unless otherwise instructed. It will find all references on the subject whether the word appears in the title, abstract, the notes, or any other location. You may limit the search to author, year, and the like, but the search is so fast that this is not usually necessary. A Boolean logic is used for complex searches. An unlimited number of search terms can be joined by "and," "or," and "not." For example, a search through a 600-reference data base for articles on trabeculectomy "or" iridotomy "and" apraclonidine "and" 1989 yielded one article and took about two seconds. The speed at which the program searches is astounding. The data base is designed to hold 32,000 references.

The second feature of EndNote Plus is its ability to create bibliographies. When working on a manuscript, EndNote can be kept open and running in the corner of the screen. On the Macintosh this can be done as a desk accessory or as a separate application. As information is typed into the word processor, one simply copies and pastes the references from EndNote Plus into the word processing document. This places a bracketed reference statement with the author's last name, the year, and a reference number at the location of the citation. Upon completion of a manuscript, a journal style is selected, and EndNote Plus is instructed to format the paper. Within moments a version of the paper appears with each reference typed out in the bibliography and cited in the text just the way the journal wants it. One does need to customize EndNote Plus for the major ophthalmic journals, but this is not challenging.

A separate add-on program, End Link, makes it possible to transfer data from on-line bibliographic data bases such as BRS into EndNote Plus.

I have been using this program for six months, and I am still delighted by what it can do for me and amazed at how quickly and effectively it can be done.

Books Received

The Best in Medical Humor. By Howard J. Bennett. Philadelphia, Hanley & Belfus, 1991. 228 pages, index, illustrated. \$25

This book is lots of fun, and years from now it will still be fun. It is the kind of book that smiles at you from the shelf, reminding you of some favorite pieces. The only way you can be sure you will be able to find these gems in the future is to buy your own copy of the book. Friends will often borrow it to copy a page here and there, so write your name firmly on the endpaper to guide it back to you.

To compile this anthology, Dr. Bennett has sifted through a lot of funny stuff and chosen the pieces he liked best. The ones he did not have room for, he has enticingly described at the end of each chapter. I'm tempted to look up "Freud's Own Cookbook," for example, just to see what is in "Slips of the Tongue in Madeira Sauce," or "Fettucine Libido."

Funny writing cannot get away with being just occasionally witty, it has to be consistently on the mark. One clinker can shatter the illusion and ruin the effect of the whole piece. So you know that these contributions have been lovingly buffed and burnished by some talented people. As Ben Milder says on page 92, "envy has me in its grip . . ."

There is not much mean spiritedness in this book; most of the pieces seem to have been inspired by some sense of exasperation, perhaps because the author recognized the situation, saw how badly it had been handled, and knew from personal experience how to avoid the problem. Rather than pontificating, railing, or wheedling to teach the lesson, the author chose to use irony, satire, and good clean fun. The result is that a larger and happier readership will take home the nourishing advice and kindly wisdom that is buried in these pages.

Eye Care in Developing Nations, ed. 2. By Larry Schwab. New York, Oxford University Press,

1990. Softcover, 204 pages, index, illustrated. \$15.95

A new edition of a popular, practical guide to ophthalmic care under difficult conditions, with illustrations showing how to break a razor blade into six surgical knives and how to use the handle of a kitchen spoon to protect the globe during eyelid surgery.

The Eye in Systemic Disease, ed. 2. By Jack J. Kanski and Dafydd J. Thomas. Stoneham, MA, Butterworths, 1990. 161 pages, index, illustrated. \$80

The Kanski-Butterworth combination usually means excellent photographs, clear color diagrams by Tarrant, and a skillful use of white space on the page that encourages the browsing eye. This volume does not disappoint.

Graves' Ophthalmopathy. Edited by Jack R. Wall and Jacques How. St. Louis, Mosby-Year Book, 1990. 196 pages, index, illustrated. \$49.95

This small volume offers 15 chapters written by an international array of experts on the pathogenesis, diagnosis, and management of Graves' ophthalmopathy. Physicians who treat these patients will want to know what is new in orbital irradiation, surgical decompression, and plasmapheresis and all the latest thoughts on orbital connective tissue antibodies.

How to Write and Publish Papers in the Medical Sciences, ed. 2. Edited by Edward J. Huth. Baltimore, Williams & Wilkins, 1990. 252 pages, index. \$29.95

This book, written by the well-known editor of the *Annals of Internal Medicine*, is a must for every aspiring academic. There is good advice on every page: how to ask yourself some tough questions about your project, such as "So what?" and "Who cares?"; how to search the literature; how to write for permission to use a figure; and how to revise your prose for fluency, clarity, accuracy, economy, and grace.

Les Strabismes. Tome Premier. Les Divergences Oculaires. By R. Pigassou-Albouy. Paris, Masson, 1990. 218 pages, index, illustrated. (No price given)

This work is the first volume of a trilogy devoted to binocularity and its disturbances; the second volume will be about convergence problems and the third will discuss strabismic amblyopia. An unusual amount of thought appears to have gone into the structure of this book. Each chapter ends with comments on how the ideas just discussed impinge upon the daily practice of pediatric ophthalmology.

Ophthalmology Oral History Series. A Link With Our Past. An Interview With David Glendenning Cogan, M.D. By Sally Smith Hughes. San Francisco, The Foundation of the American Academy of Ophthalmology, 1990. Softcover, 256 pages, index, illustrated. \$55

These oral histories make fascinating reading, partly because the subjects have had long and active lives that touched on the lives of many others and partly because the personalities come through in the recorded conversation. Sally Hughes, the interviewer, is alert, cheerful, and well informed, and in this volume we get glimpses of Dr. Cogan's wide-ranging knowledge, his modest view of his tremendous accomplishments, and the irrepressibility of his impish wit.

Optics, Physiology and Vision. Edited by Suzanne P. McKee and Ken Nakayama. Elmsford, NY, Pergamon Press, 1990. 1921 pages, index, illustrated. \$45

This is a reprint, in hardcover, of the November 1990 issue of *Vision Research*, a special 400-page issue that was prepared as a festschrift for Gerald Westheimer on his 65th birthday.

Phacoemulsification Surgery. Edited by Terence M. Devine and William Banko. Elmsford, NY, Pergamon Press, 1990. 130 pages, index, illustrated. \$125

This is a practical guide to phacoemulsification surgery with contributions by 11 well-known anterior segment surgeons. It has good, clean illustrations and is pleasantly laid out.

The Book List

Color Atlas of Lens Implantation. Edited by Piers Percival. St. Louis, Mosby-Year Book, 1991. 317 pages, index, illustrated. \$140

Immediate Eye Care. By Nicola K. Ragge and David L. Easty. St. Louis, Mosby-Year Book, 1990. 228 pages, index, illustrated. \$89

The Neurology of Eye Movements. By R. John Leigh and David S. Zee. Philadelphia, F. A. Davis, 1991. 561 pages, index, illustrated. \$80

USP DI, ed. 11, vol. 1. Drug Information for the Health Care Professional. Rockville, Maryland, United States Pharmacopeial Convention, 1991. 3,304 pages, index, illustrated. \$110

USP DI, ed. 11, vol. 2. Advice for the Patient. Rockville, Maryland, United States Pharmacopeial Convention, 1991. 1,624 pages, index, illustrated. \$42

USP DI, ed. 11, vol. 3. Approved Drug Products and Legal Requirements. Rockville, Maryland, United States Pharmacopeial Convention, 1991. 1,016 pages, index, illustrated. \$75

Walsh and Hoyt's Clinical Neuro-Ophthalmology, ed. 4, vol. 4. By Neil R. Miller. York, Pennsylvania, Williams & Wilkins, 1991. 2,820 pages, index, illustrated. \$150

ABSTRACT DEPARTMENT

Edited by Michael A. Kass, M.D.

Clinical and magnetic resonance imaging in optic neuritis. Jacobs, L.*, Munschauer, F. E., and Kaba, S. E.: *Neurology* 41:15, 1991.

OPTIC NEURITIS, MAGNETIC RESONANCE IMAGING SCANS, SILENT BRAIN LESIONS, MULTIPLE SCLEROSIS

A cohort of 48 patients with isolated monosymptomatic optic neuritis underwent magnetic resonance imaging of the brain. The magnetic resonance imaging scans disclosed that 23 of the 48 patients (48%) had clinically silent brain lesions consistent with multiple sclerosis. During four years of follow-up, nine patients developed clinical multiple sclerosis. Six of these nine patients had abnormal magnetic resonance images; the other three patients had normal magnetic resonance images both initially when they had optic neuritis only and later after they had developed multiple sclerosis. The other 17 patients with abnormal magnetic resonance images did not develop the signs or symptoms of multiple sclerosis during the follow-up period. Thus, an abnormal magnetic resonance image in an individual who has optic neuritis does not indicate that multiple sclerosis will definitely develop within a four-year follow-up period. Conversely, normal magnetic resonance imaging in such patients does not mean that they will not develop disseminated disease. It is not appropriate to make a diagnosis of multiple sclerosis in a patient who has monosymptomatic optic neuritis and an abnormal magnetic resonance image without other laboratory-confirmed abnormalities.—Michael A. Kass

*Department of Neurology, Buffalo General Hospital, 100 High St., Buffalo, NY 14203.

Central nervous system involvement in Von Hippel-Lindau disease. Filling-Katz, M. R.*, Choyke, P. L., Oldfield, E., Charnas, L., Patronas, N. J., Glenn, G. M., Gorin, M. B., Morgan, J. K., Linehan, W. M., Seizinger, B. R., and Zbar, B.: *Neurology* 41:41, 1991.

VON HIPPEL-LINDAU DISEASE, CENTRAL NERVOUS SYSTEM TUMORS

Von Hippel-Lindau disease is a dominantly inherited disorder characterized by hemangioblastomas of the central nervous system, retinal angiomas, and multiple cysts and tumors of the viscera. Fifty individuals with Von Hippel-Lindau disease were studied with gadolinium-enhanced magnetic resonance imaging to determine the frequency and distribution of central nervous system lesions. Of the 50 patients, 36 (72%) had one or more central nervous system tumors. The most frequently affected sites in the central nervous system, excluding the retina, were the cerebellum, spinal cord, and brain stem. Lesions were particularly common in the craniocervical junction and the conus medullaris. Many of the patients had more than one lesion, and 41% of the patients with central nervous system tumors were neurologically asymptomatic. Nine of the patients in this series were noted to have nystagmus, and one patient had papilledema related to hydrocephalus. The authors recommend that all patients age 10 years or older at risk for Von Hippel-Lindau disease should be examined with gadolinium-enhanced magnetic resonance imaging.—Michael A. Kass

*Room 3C102, Bldg. 10, NIAAA, 9000 Rockville Pike, Bethesda, MD 20892.

Second eye involvement in age-related macular degeneration. A four-year prospective study. Roy, M.*, and Kaiser-Kupfer, M.: *Eye* 4:813, 1990.

MACULAR DEGENERATION, FELLOW EYES

Clinical studies have shown that age-related macular degeneration often involves both eyes of affected individuals. A prospective study was done of 41 patients who had either exudative or advanced atrophic age-related macular degeneration in one eye with visual acuity of 20/80 or worse. The fellow eyes had best-corrected visual acuity of 20/30 or better and either macular drusen (with or without localized hypo- or hyperpigmentation) or atrophy of the retinal pigment epithelium but no evidence of subretinal neovascularization or previous laser treatment. The cumulative risk of developing

either exudative age-related macular degeneration or atrophic age-related macular degeneration and visual acuity of 20/80 or worse in the fellow eye was 23% at four years. The authors estimated that 90% of their patients wore yellow lenses to protect their eyes. The involvement of the second eyes in this report is lower than in many previous reports. It is not clear whether this lower incidence can be attributed to protection from yellow lenses or to sampling variation.—Michael A. Kass

*University of Medicine and Dentistry, New Jersey Medical School, Department of Ophthalmology, 15 S. Ninth St., Newark, NJ 07107.

Carotid endarterectomy for chronic retinal ischemia. Rubin, J. R.*, McIntyre, K. M., Lukens, M. C., Plecha, E. J., and Bernhard, V. M.: *Surg. Gynecol. Obstet.* 171:497, 1990.

OCULAR ISCHEMIA, CAROTID ENDARTERECTOMY

Carotid arterial disease may produce a variety of ischemic ocular problems that can eventually lead to permanent blindness. From 1984 to 1988, 18 patients underwent carotid artery reconstruction in an attempt to reverse or prevent progression of ischemic oculopathy. During a mean follow-up period of 21 months after carotid arterial reconstruction, subjective improvement in vision as well as a resolution in ocular and periorbital pain was reported in 16 of the patients (89%). Additionally, visual acuity improved or stabilized in 17 (94.4%), macular photostress recovery times improved in 16, and ophthalmoscopic examinations demonstrated improvement or resolution of ischemic signs in 17 of the patients. One patient had recurrent episodes of amaurosis fugax, which resolved after two weeks and did not recur. Another patient developed neovascular glaucoma with visual deterioration. The authors concluded that carotid arterial reconstruction is an effective treatment for ischemic oculopathy and is most beneficial if performed early, before the onset of irreversible neovascular glaucoma.—Michael A. Kass

*Department of Surgery, Case Western Reserve University, 2074 Abington Rd., Cleveland, OH 44106.

How satisfying is the practice of internal medicine? A national survey. Lewis, C. E.*, Prout, D. M., Chalmers, E. P., and Leake, B.: *Ann. Intern. Med.* 114:1, 1991.

PHYSICIAN SATISFACTION, ADMINISTRATIVE BURDENS, LITIGATION, INCOME, AUTONOMY

Several signs indicate that medicine in general, and internal medicine in particular, is losing its attractiveness as a career. Members of the American College of Physicians were surveyed about their level of satisfaction and sources of dissatisfaction with medical practice. The authors collected responses from 1,446 physicians (64% of those surveyed), and 1,290 of these responses were usable. More than 80% of the respondents were satisfied with their professional challenges, opportunities to interact with colleagues, and relationships with patients. Only about half, however, were satisfied with their potential income, and most internists were dissatisfied with the loss of control over clinical decision making. Major sources of concern were administrative burdens, the threat of malpractice litigation, loss of income, and loss of clinical autonomy. Forty percent of the internists stated that they now discourage students from careers in internal medicine. Only 39% of the internists stated that they would once again pursue a career in internal medicine. Many respondents stated that they were concerned about access to medical care. In this regard, 18% of the internists had many patients without health care insurance, 69% had some patients without coverage, and 61% had some patients who had lost their insurance because of changing jobs or location. The physicians believed that universal access to health care was the cornerstone to health care reform.—Michael A. Kass

*Division of General Internal Medicine, B-558 Factor Bldg., Department of Medicine, UCLA School of Medicine, Los Angeles, CA 90024-1685.

Medical malpractice—the Canadian experience. Coyte, P. C.*, Dewees, D. N., and Trebilcock, M. J.: *N. Engl. J. Med.* 324:89, 1991.

MALPRACTICE LITIGATION, CANADIAN AND AMERICAN EXPERIENCES

Canadian physicians are one fifth as likely to be sued for malpractice as their American counterparts. This difference is attributable to a number of legal and institutional factors in Canada, including universal health insurance, more generous programs of social welfare, limited use of contingency fees, the practice of having the losing party bear the cost of litigation, limited awards for pain and suffering, infrequent use of juries, the effective work of the Canadian Medical Protective Association, and a less litigious culture.

Despite these considerable differences, the number of claims per physician is growing at a similar rate in the United States and Canada. It follows that the increase in malpractice liability in the United States cannot solely be the result of unique aspects of the United States legal system. The authors hypothesize that advances in medical technology have increased the vulnerability of physicians to lawsuits, even though the advances have improved patient care. People seem to have become less willing to bear risks, and this changed social attitude, combined with a less personal patient-physician relationship, has led to an increased number of claims in both countries.

Although litigation is less common in Canada, Canadian physicians seem to respond similarly to the situation and have been noted to withdraw services, undertake more discussions with their patients, keep more records, and undertake programs of institutional risk management.—Michael A. Kass

*Department of Health Administration, 2nd Fl., McMurrich Bldg., Faculty of Medicine, University of Toronto, Toronto, Ontario M5S 1A8, Canada.

Incidence of adverse events and negligence in hospitalized patients. Results of the Harvard Medical Practice Study I. Brennan, T. A.*, Leape, L. L., Laird, N. M., Hebert, L., Localio, A. R., Lawthers, A. G., Newhouse, J. P., Weiler, P. C., and Hiatt, H. H.: *N. Engl. J. Med.* 324:370, 1991.

ADVERSE EVENTS, MEDICAL NEGLIGENCE, SUBSTANDARD CARE

As part of an interdisciplinary study of medical injury and malpractice litigation, the au-

thors reviewed 30,121 randomly selected records from 51 randomly selected acute care, nonpsychiatric hospitals in New York State. They then developed population estimates of injuries and computed rates according to the age and sex of the patients as well as the specialties of the physicians. Adverse events occurred in 3.7% of the patients (95% confidence interval, 3.2% to 4.2%). In turn, 27.6% of the adverse events were caused by negligence (95% confidence interval, 22.5% to 32.6%). Although 70.5% of the adverse events resulted in disability lasting less than six months, 2.6% caused permanently disabling injuries, and 13.6% led to death. Using weighted totals, the authors estimated that among the 2,671,863 patients discharged from New York hospitals in 1984 there were 98,609 adverse events and 27,179 adverse events involving negligence. Adverse events were more common in older patients, and the percentage of adverse events caused by negligence also increased with patient age. There were significant differences in rates of adverse events among categories of clinical specialties but no differences in the percentage caused by negligence.—Michael A. Kass

*Division of General Medicine, Brigham and Women's Hospital, 75 Francis St., Boston, MA 02115.

The nature of adverse events in hospitalized patients. Results of the Harvard Medical Practice Study II. Leape, L. L.*, Brennan, T. A., Laird, N., Lawthers, A. G., Localio, A. R., Barnes, B. A., Hebert, L., Newhouse, J. P., Weiler, P. C., and Hiatt, H. H.: *N. Engl. J. Med.* 324:377, 1991.

ADVERSE EVENTS, MEDICAL NEGLIGENCE, SUBSTANDARD CARE

A cohort of 30,195 randomly selected hospital records were examined, and 1,133 patients (3.7%) were identified with disabling injuries caused by medical treatment. Two physician-reviewers independently identified the adverse events and evaluated them with respect to negligence, errors in management, and extent of disability. Drug complications were the most common type of adverse event (19%), followed by wound infections (14%), and technical com-



plications (13%). Nearly half of the adverse events (48%) were associated with an operation. Adverse events during surgery were less likely to be caused by negligence (17%) than were nonsurgical ones (37%). The proportion of adverse events caused by negligence was highest for diagnostic mishaps (75%), noninvasive therapeutic mishaps (77%), and events occurring in the emergency room (70%). Errors in management were identified for 58% of the adverse events, among which nearly half were attributed to negligence. The authors propose that a high proportion of adverse events are caused by management errors and thus are potentially preventable.—Michael A. Kass

*Harvard School of Public Health, 677 Huntington Ave., Boston, MA 02115.

Comparison of uninsured and privately insured hospital patients. Condition on admission, resource use, and outcome. Hadley, J.*, Steinberg, E. P., and Feder, J.: JAMA 265:374, 1991.

HEALTH INSURANCE, MORTALITY, HEALTH CARE COSTS

To investigate the association between insurance status and condition on admission, resource use, and in-hospital mortality, we analyzed discharge abstracts for 592,598 patients hospitalized in 1987 in a national sample of hospitals. In 13 of 16 age-sex-race-specific cohorts, the uninsured had a 44% to 124% higher risk of in-hospital mortality at the time of admission than did the privately insured. After controlling for this difference, the actual in-hospital death rate was 1.2 to 3.2 times higher among uninsured patients in 11 of 16 cohorts. The uninsured also were 29% to 75% less likely to undergo each of five high-cost or high-discretion procedures and 50% less likely to have normal results on tissue pathology reports for biopsies performed during five of seven different endoscopic procedures. Our results suggest that insurance status is associated with a broad spectrum of aspects of hospital care.—Authors' abstract

*Center for Health Policy Studies, 2233 Wisconsin Ave. N.W., Ste. 525, Washington, DC 20007.

The orphan drug act. The first 7 years. Asbury, C. H.*: JAMA 265:893, 1991.

ORPHAN DRUGS, LEGISLATION

The 1983 Orphan Drug Act sought to increase market incentives and decrease regulatory barriers for products used to treat rare ("orphan") diseases. Major provisions included market exclusivity, tax credits, and regulatory process clarifications. This analysis compares pre- and post-Act industry and government data to examine changes associated with the law. While industry sponsored 34 marketed and 24 experimental orphan drugs in the 17 years prior to the Act, it has sponsored 39 of 42 marketed orphan products in the 7 years since the Act. An additional 301 experimental products have orphan designation. While 25 of 40 marketed orphan products reportedly had annual sales of less than \$1 million, product sales for three conditions are more than \$100 million annually. This prompted changes in the law, passed by Congress in 1990, but vetoed. Overall, the law has been associated with an increase in orphan product development. The law's costs and benefits to companies, patients, and the public should be examined if future changes are proposed.—Author's abstract

*Robert Wood Johnson Foundation, P.O. Box 2316, Princeton, NJ 08543-2316.

Hispanic health in the United States. Council on Scientific Affairs*: JAMA 265:248, 1991.

HISPANIC POPULATION, HEALTH STATUS

Hispanics are the fastest growing minority in the United States. Typically, they are divided into five subgroups: Mexican American, Puerto Rican, Cuban American, Central or South American, and "other" Hispanics. Risk factors for morbidity and mortality vary among these subgroups. Use of health care services is affected by perceived health care needs, insurance status, income, culture, and language. Compared with whites, Hispanics are more likely to live in poverty, be unemployed or underemployed, and have little education and no private insurance. Hispanics are at an increased risk for certain medical conditions, including diabetes,

hypertension, tuberculosis, human immunodeficiency virus infection, alcoholism, cirrhosis, specific cancers, and violent deaths. Proportionate to their representation in the population, there are few Hispanic health providers, emphasizing the need for all medical personnel to be knowledgeable about Hispanic health care needs.—Authors' abstract

*Council on Scientific Affairs, American Medical Association, 515 N. State St., Chicago, IL 60610.

Maternal outcome after open fetal surgery. A review of the first 17 human cases. Longaker, M. T., Golbus, M. S., Filly, R. A., Rosen, M. A., Chang, S. W., and Harrison, M. R.*: JAMA 265:737, 1991.

OPEN FETAL SURGERY, HYDRONEPHROSIS, CONGENITAL DIAPHRAGMATIC HERNIA

A few fetal diseases may benefit from surgical treatment before birth, but hysterotomy and subsequent delivery by cesarean section pose a risk to the otherwise unaffected mother. To assess maternal risk of mortality, morbidity, and reproductive potential after fetal surgery, we reviewed our experience with 17 highly selected women who underwent fetal surgery. Fifteen of these procedures were performed for one of two congenital anomalies: severe bilateral hydronephrosis and congenital diaphragmatic hernia. There were no deaths or serious maternal injuries. In the 14 women who continued pregnancy after hysterotomy, uterine irritability and preterm labor were frequent complications, requiring early confinement in most cases. There has been no detectable effect on future fertility, as indicated by eight subsequent normal pregnancies. We conclude that hysterotomy for fetal surgery can be accomplished without unduly endangering the mother's life or her future reproductive potential. However, morbidity related to premature labor remains a serious problem, and our ability to control uterine contractions after hysterotomy remains the limiting factor in human fetal surgery.—Authors' abstract

*Department of Surgery, University of California (San Francisco), Third and Parnassus Aves., Rm. 585-HSE, San Francisco, CA 94143-0570.

Head shaking by visually impaired children. A voluntary neurovisual adaptation which can be confused with spasmodic nutans. Jan, J. E.*, Groeneweld, M., and Connolly, M. B.: Dev. Med. Child Neurol. 32:1061, 1990.

HEAD SHAKING, NYSTAGMUS, IMPROVED VISUAL ACUITY

It is well known that visually impaired individuals with nystagmus may exhibit rapid horizontal and pendular head shaking during periods of intense visual fixation. The authors systematically studied 260 children who had nystagmus and visual impairment caused by congenital ocular abnormalities and 13 children with motor nystagmus. Eighteen children (6.6%) were noted to have head shaking. In every case the head shaking followed the appearance of nystagmus by months or even years during early childhood. Head shaking occurred in bursts lasting from five to 30 seconds and only occurred during intense visual fixation. The head shaking did not spread to involve any other part of the body. Head shaking appeared to be a subconscious act, but once attention was called to this behavior, it could be started and stopped at will. The rate of head oscillations seemed to be equal to the rate of nystagmus. Thus, head shaking appeared to be a voluntary, learned neurovisual adaptation to improve visual acuity. The authors propose that the head oscillations compensate for the nystagmus and help to maintain the visual image on the fovea.—Michael A. Kass

*Division of Pediatric Neurology, University of British Columbia, 4480 Oak St., Vancouver, British Columbia, V6H 3V4.

Spontaneous inflammatory disease in transgenic rats expressing HLA-B27 and human $\beta_2\text{m}$. An animal model of HLA-B27-associated human disorders. Hammer, R. E.*, Maika, S. D., Richardson, J. A., Tang, J.-P., and Taurog, J. D.: Cell 63:1099, 1990.

HLA-B27, RHEUMATIC DISEASES, ANIMAL MODEL

HLA-B27, a serologically defined allele of the human HLA-B locus, is of interest because it is associated with a group of relatively common inflammatory disorders, including ankylosing

spondylitis, reactive arthritis, juvenile spondyloarthritis, psoriatic arthropathy, and enteropathic arthropathy. These disorders are often classified as rheumatic diseases because of prominent musculoskeletal manifestations, but they also involve multiple organ systems, including the gastrointestinal tract, genitourinary tract, skin, eyes, and heart.

To investigate the role of HLA-B27 in these disorders, the human HLA-B27 and β_2 -microglobulin genes were introduced into rats, a species known to be susceptible to experimentally induced inflammatory diseases. Rats from one transgenic line spontaneously developed inflammatory disease involving the gastrointestinal tract, peripheral and vertebral joints, male genital tract, skin, nails, heart, and eyes. This pattern of organ system involvement showed a striking resemblance to the HLA-B27-associated human disorders. These results suggest that HLA-B27 plays a central role in the pathogenesis of the inflammatory rheumatic diseases. The availability of this animal model should further research in these disorders.—Michael A. Kass

*Howard Hughes Medical Institute, University of Texas Southwestern Medical Center, Dallas, TX 75235.

Effect of a resutured iridotomy on glare disability in glaucoma patients having cataract surgery. Cahane, M.*, Glovinsky, Y., and Blumenthal, M.: *J. Cataract Refract. Surg.* 17:58, 1991.

CATARACT SURGERY, SECTOR IRIDOTOMY, POSTOPERATIVE GLARE

The authors studied 22 patients with glaucoma who had fixed miotic pupils before cataract surgery. The patients were divided, retrospectively, into a group in which the sector (radial) iridotomy was sutured after intraocular lens insertion and a second group in which the sector iridotomy was not sutured. The two groups were matched for age, sex, average duration of glaucoma, type of glaucoma, operative technique, mean follow-up period, intraocular pressure, and cup/disk ratio. Glare disability was measured with the Miller-Nadler technique. A similar reduction in visual acuity un-

der glare was found in the two groups: 0.55 ± 1.2 and 0.45 ± 0.9 Snellen lines, respectively. The glare-induced reduction in visual acuity correlated with the opacification of the posterior capsule but not with the functional pupillary area. The authors concluded that suturing sector iridotomies does not reduce postoperative glare.—Michael A. Kass

*Maurice and Gabriela Goldschleger Eye Institute, Chaim Sheba Medical Center, Tel Hashomer 52621, Israel.

Long-term efficacy of primary laser trabeculoplasty. Elsås, T.*, and Johnsen, H.: *Br. J. Ophthalmol.* 75:34, 1991.

LASER TRABECULOPLASTY, PRIMARY TREATMENT FOR GLAUCOMA

Sixty patients each received laser trabeculoplasty to one eye as the initial treatment for glaucoma. Of these individuals, 42 had capsular glaucoma and 18 had primary open-angle glaucoma. Each patient received 100 burns scattered over the entire circumference of the trabecular meshwork in one or two sessions. The mean prelaser intraocular pressure was 35.2 ± 6.5 mm Hg. Successful treatment was defined as intraocular pressure of less than 22 mm Hg without medication. The probability of success was 0.73 at one year, 0.68 at two years, 0.57 at three years, and 0.50 at four years. There was a high failure rate during the first month after treatment, presumably because eyes did not respond to laser treatment. If treatment was successful at one month, the probability of success at four years was 0.63. Three eyes developed progressive visual field loss or progressive cupping despite a mean intraocular pressure of less than 22 mm Hg without medication. High prelaser intraocular pressure and severe visual field defects were significant predictors of treatment failure. The authors suggest that laser trabeculoplasty should be considered as an alternative to medication for the initial treatment of glaucoma. They believe treatment is easy to perform, the rate of complications is low, and successful treatment removes the need for compliance with medication. They warn that this approach may not be appropriate in eyes with high prelaser intraocu-

lar pressures or severe visual field loss.—Michael A. Kass

*Department of Ophthalmology, University of Trondheim, N-7006, Trondheim, Norway.

Acetazolamide-associated aplastic anemia.

Keisu, M.*, Wiholm, B.-E., Öst, Å., and Mortimer, Ö.: *J. Intern. Med.* 228:627, 1990.

ACETAZOLAMIDE, ADVERSE DRUG REACTIONS, APLASTIC ANEMIA

Eleven cases of acetazolamide-associated aplastic anemia were reported in Sweden during a 17-year period. There were six women and five men with a median age of 71 years (range 63–85 years). The median dose of acetazolamide was 500 mg, and the median duration of treatment was 3 months (range 2–71 months). Ten of the eleven patients died, all within 8 weeks after detection of their aplastic anemia. The relative risk of developing aplastic anemia when taking acetazolamide was 13.3 (95% confidence limits (CL); 6.8–25.3). The estimated incidence of reported acetazolamide-associated aplastic anemia is approximately one in 18,000 patient years. The results strongly indicate that acetazolamide treatment is associated with a substantial increase in the risk of developing aplastic anemia.—Authors' abstract

*Department of Clinical Pharmacology, Huddinge University Hospital, 14186 Huddinge, Sweden.

Zidovudine-induced macular edema. Lalonde, R. G.*, Deschênes, J. G., and Seamone, C.: *Ann. Intern. Med.* 114:297, 1991.

ZIDOVUDINE, MACULAR EDEMA

Zidovudine has become the standard therapy for patients with altered immunity caused by human immunodeficiency virus. More recently, zidovudine was shown to be effective in treating asymptomatic HIV-infected patients with low helper T-cell levels. The authors examined a 42-year-old man who had low-grade anterior uveitis. The patient had previously been treated for secondary syphilis. Subsequently the pa-

tient developed two episodes of macular edema that were documented by fluorescein angiography. On both occasions cystoid macular edema began within a few days of starting zidovudine therapy. Zidovudine was discontinued, and visual acuity improved to pretreatment levels over a few weeks. It is not possible to be sure that zidovudine caused macular edema in this patient with multiple health problems. Macular edema, however, occurred after institution of the therapy and cleared after the cessation of the therapy on two occasions. Ophthalmologists should be aware of this potential drug-induced complication.—Michael A. Kass

*Infectious Diseases Clinic, Royal Victoria Hospital, 687 Pine Ave., Montreal, Quebec H3A 1A1.

Fifteen-year argon laser and xenon photocoagulation results of Bascom Palmer Eye Institute's patients participating in the Diabetic Retinopathy Study. Blankenship, G. W.*: *Ophthalmology* 98:125, 1991.

DIABETIC RETINOPATHY, PHOTOCOAGULATION

Fifteen years after panretinal photocoagulation in the Diabetic Retinopathy Study, 86 (57%) patients had died, 14 (9%) could not be located, and 51 (34%) of 151 patients were examined to determine the long-term treatment effects. Of the eyes randomized to photocoagulation only 1 (5%) of 19 argon-treated and 1 (3%) of 32 xenon-treated eyes had received additional laser treatment, but 8 argon-treated and 7 xenon-treated eyes had had cataract removal. Eleven (58%) of the initially argon-treated and 13 (41%) of the initially xenon-treated eyes had 20/40 or better acuity, and 18 (95%) of the initially argon-treated and 26 (82%) of the initially xenon-treated eyes had 20/200 or better acuity. Of the control eyes 17 (33%) had 20/40 or better, and 30 (58%) had 20/200 or better acuity. Argon and xenon panretinal photocoagulation for diabetic retinopathy provide good results for at least 15 years.—Author's abstract

*College of Medicine, University Hospital, Milton S. Hershey Medical Center, P.O. Box 850, Hershey, PA 17033.

Ophthalmic complications of amniocentesis. Naylor, G., Roper, J. P., and Willshaw, H. E.*: Eye 4:845, 1990.

AMNIOCENTESIS, OCULAR INJURY

Amniocentesis is generally considered safe, although there are scattered reports of fetal damage caused by this procedure. There are relatively few reports of ocular injury. The authors examined three patients subjected to amniocentesis who had signs of anterior segment penetrating trauma soon after birth. One patient had a limbal scar, one had an adherent leukoma, and one had a full-thickness corneal

scar with a peaked pupil. Additionally, a fourth patient was noted to have a chorioretinal scar with an overlying vitreous condensation in the temporal periphery. A fifth patient had a homonymous hemianopsia and a gaze palsy thought to be caused by central nervous system injury. The authors suggest that ocular damage during amniocentesis may be more common than reports suggest and should be considered in cases of congenital ocular abnormalities.—Michael A. Kass

*Eye Department, Birmingham Childrens Hospital, Ladywood Middleway, Birmingham B16 8ET.

NEWS ITEMS

**Send News Items to
American Journal of Ophthalmology
435 N. Michigan Ave., Suite 1415
Chicago, IL 60611**

The Journal invites readers to submit announcements concerning meetings, postgraduate courses, lectures, honors, and appointments. Each item must be typed double-spaced on bond paper with 1½-inch margins. Only one news item should be submitted on each page. Announcements concerning meetings and courses must contain the title, location, dates, sponsors, and address required for additional information. Each item must not exceed 75 words in length and be prepared in narrative, not outline, form. Announcements of meetings and courses must be received at least four months before the event.

**University of Aberdeen Medical School,
Scotland: Second International Symposium
on Recent Developments in the
Immunopathology of Intraocular
Inflammation**

The University of Aberdeen Medical School, Scotland, will hold the Second International Symposium on Recent Developments in the Immunopathology of Intraocular Inflammation in Aberdeen, United Kingdom, Oct. 22–25, 1991. For more information, write Prof. John V. Forrester, M.D., University of Aberdeen Medical School, Department of Ophthalmology, Foresterhill, Aberdeen AB9 2DY, Scotland; fax (0224) 685158.

**Alcon Surgical: San Diego Fluorescein and
Laser Workshop for General
Ophthalmologists**

Alcon Surgical, Inc., will sponsor the San Diego Fluorescein and Laser Workshop for General Ophthalmologists, July 12 and 13, 1991, at the Hotel del Coronado, San Diego. For further information, write Tara Wilson, 12630 Monte Vista Rd., Ste. 104, Poway, CA 92064; telephone (619) 451-1911.

**American College of Veterinary
Ophthalmologists: Annual Meeting**

The American College of Veterinary Ophthalmologists will meet Sept. 26–29, 1991, in Boston, Massachusetts. For further information, write Dr. Randall H. Scagliott, Sacramento Animal Medical Group, 4990 Manzanita Ave., Carmichael, CA 95608.

**Bethesda Eye Institute/St. Louis University:
Small Incision Cataract Surgery**

The Bethesda Eye Institute/St. Louis University and Storz Ophthalmics will sponsor a symposium, "Small Incision Cataract Surgery," in Teaneck, New Jersey, July 11, 1991. For more information, write Laura Clatch, Storz Ophthalmics, 3365 Tree Court Industrial Blvd., St. Louis, MO 63122; telephone (800) 325-9929, ext. 5633.

**University of California and the Proctor
Foundation: Uveitis/Retinal Frontiers**

The University of California in San Francisco and the Proctor Foundation will sponsor Uveitis/Retinal Frontiers: Diagnostic, Medical, and Surgical Approaches, Sept. 13–15, 1991, at Carmel Valley Ranch Resort in Carmel, California. For more information, write the University of California, Extended Programs in Medical Education, Room LS-105, San Francisco, CA 94143-0742; telephone (415) 476-4251; fax (415) 476-0318.

Indianapolis Ophthalmological Society

The Indianapolis Ophthalmological Society has scheduled three fall meetings to be held Sept. 17, Oct. 15, and Nov. 19, 1991, at the Westin Hotel in Indianapolis. For more information, write Louis Cantor, M.D., Department of Ophthalmology, Indiana University School of Medicine, 702 Rotary Circle, Indianapolis, IN 46202.

**University Eye Clinic of Jena, Germany:
Endogenous Ocular Inflammations—Uveitis
'91**

The University Eye Clinic of Jena, Germany, will hold an international symposium on "Endogenous Ocular Inflammations—Uveitis '91," Oct. 2–6, 1991, in Weimar/Thuringia, sponsored by the Thuringian Ophthalmological Society. For further information, write Prof. S. Klein, Department of Ophthalmology, Bachstr. 18, D-06900 Jena, Germany.

Alcon Research Institute: Awards

The Alcon Research Institute, an entity dedicated to vision research, is funded by Alcon Laboratories, Inc. It is directed by a fully inde-

pendent advisory committee comprised of the following: Steven M. Podos, M.D. (Chairman), Mount Sinai School of Medicine, New York, New York; Anders Bill, M.D., Uppsala Universitets Biomedicum, Uppsala, Sweden; Hans Bloemendal, Ph.D., Universiteit Van Nijmegen, The Netherlands; Henry F. Edelhauser, Ph.D., Emory University School of Medicine, Atlanta, Georgia; Morton F. Goldberg, M.D., Wilmer Institute, Johns Hopkins University School of Medicine, Baltimore, Maryland; Yoshiaki Kitazawa, M.D., Gifu University School of Medicine, Gifu, Japan; Howard M. Leibowitz, M.D., Boston University Medical Center, Boston, Massachusetts; Elke Lutjen-Drecoll, M.D., University Erlangen-Nuernberg, Erlangen, Germany; Neville N. Osborne, Ph.D., University of Oxford, Oxford, England; and Abraham Spector, Ph.D., Columbia University, New York, New York.

Each year the committee nominates individuals, who have made important contributions to vision research, to receive a financial award with the expectation that the awardees will apply it to further their research.

An award of \$60,000 was given to each of the following scientists in 1991: Jules Baum, M.D., Tufts-New England Medical Center, Boston, Massachusetts; Denis A. Baylor, M.D., Stanford Medical School, Stanford, California; S. S. Bhattacharya, M.Sc., Ph.D., Department of Human Genetics, Newcastle-Upon-Tyne, England; Alan Wright, Ph.D., Western General Hospital, Edinburgh, Scotland (Shastid Award); James P. Dillon, Ph.D., College of Physicians and Surgeons, Columbia University, New York, New York; Josef Flammer, M.D., Universitaets-Augenklinik, Basel, Switzerland; David L. Guyton, M.D., Wilmer Institute, Johns

Hopkins University School of Medicine, Baltimore, Maryland; John R. Hassell, Ph.D., Eye and Ear Institute, University of Pittsburgh, Pittsburgh, Pennsylvania; Richard N. Lolley, Ph.D., V.A. Medical Center, Sepulveda, California; Joram P. Piatigorsky, Ph.D., National Eye Institute, Bethesda, Maryland; Robert R. Rando, Ph.D., Harvard Medical School, Boston, Massachusetts; Gunter K. von Noorden, M.D., Baylor College of Medicine, Houston, Texas; and Per Wistrand, M.D., Uppsala University, Uppsala, Sweden.

Personals

Frederick C. Blodi

Frederick C. Blodi, professor of ophthalmology at the University of Iowa Medical School, gave the First Charles Snyder Lecture at the National Institutes of Health, March 15, 1991, to honor the former librarian of the Massachusetts Eye & Ear Infirmary. Professor Blodi discussed famous personages with ocular problems.

Irene H. Maumenee

Irene H. Maumenee, professor of ophthalmology and pediatrics at the Wilmer Institute, will be honored as the first Lewis Ort Professor of Ophthalmology. She founded the Johns Hopkins Center for Hereditary Eye Diseases at Wilmer 19 years ago.

Akira Nakajima

Akira Nakajima will deliver the Third Jules François Lecture, Conquest of Blindness, Past, Present, and Future, June 22, 1991, at St. Vincent's Hospital in New York City.

Correction

In the article, "Corneal ulcer and adverse reaction rates in premarket contact lens studies" (Am. J. Ophthalmol. 111:457, April 1991), by S. M. MacRae, C. Herman, R. D. Stulting, R. Lippman, D. Whipple, E. Cohen, D. Egan, C. P. Wilkinson, C. Scott, R. Smith, and D. Phillips, the equation on page 459 was printed incorrectly. The corrected equation is reprinted below.

$$\text{Patient-years of exposure} = \frac{\text{Duration (patients completed)}}{\text{Duration (patients enrolled - patients completed)}}$$

AMERICAN JOURNAL OF OPHTHALMOLOGY®

Volume 111
JANUARY-JUNE, 1991

FRANK W. NEWELL, *Publisher and Editor-in-Chief*
435 N. Michigan Ave., Suite 1415, Chicago, Illinois 60611

EDITORIAL BOARD

JULES BAUM, *Boston*
WILLIAM M. BOURNE, *Rochester*
RONALD M. BURDE, *New York*
FRED EDERER, *Bethesda*
FREDERICK T. FRAUNFELDER, *Portland*
STEVEN G. KRAMER, *San Francisco*
IRVING H. LEOPOLD, *Irvine*
ROBERT MACHEMER, *Durham*
NANCY M. NEWMAN, *San Francisco*
DON H. NICHOLSON, *Miami*
EDWARD W. D. NORTON, *Miami*
DEBORAH PAVAN-LANGSTON, *Boston*

ALLEN M. PUTTERMAN, *Chicago*
DENNIS ROBERTSON, *Rochester*
MERLYN M. RODRIGUES, *Baltimore*
STEPHEN J. RYAN, *Los Angeles*
JERRY A. SHIELDS, *Philadelphia*
M. BRUCE SHIELDS, *Durham*
RONALD E. SMITH, *Los Angeles*
BRUCE E. SPIVEY, *San Francisco*
BRADLEY R. STRAATSMA, *Los Angeles*
E. MICHAEL VAN BUSKIRK, *Portland*
GUNTER K. VON NOORDEN, *Houston*

CONSULTING BOARD

MATHEA R. ALLANSMITH, *Boston*
CROWELL BEARD, *San Jose*
BERNARD BECKER, *St. Louis*
BENJAMIN F. BOYD, *Panama*
RONALD E. CARR, *New York*
CLAES H. DOHLMAN, *Boston*
DUPONT GUERRY III, *Richmond*
EUGENE HELVESTON, *Indianapolis*

ROBERT W. HOLLENHORST, *Rochester*
HERBERT E. KAUFMAN, *New Orleans*
ARTHUR H. KEENEY, *Louisville*
KENNETH R. KENYON, *Boston*
CARL KUPFER, *Bethesda*
ALBERT M. POTTS, *Tucson*
MARVIN L. SEARS, *New Haven*
GEORGE O. WARING, *Atlanta*

H. STANLEY THOMPSON, *Book Review Editor*
THOMAS M. AABERG, *Senior Associate Editor*
MICHAEL A. KASS, *Abstract Editor*
MARY L. BORYSEWICZ, *Executive Managing Editor*

PUBLISHED MONTHLY BY THE OPHTHALMIC PUBLISHING COMPANY
435 N. Michigan Ave., Suite 1415, Chicago, Illinois 60611

SUBJECT INDEX

Note: Abstract Index follows Author Index

A

***Acanthamoeba* sp.**

Successful medical management of *Acanthamoeba* keratitis (correspondence), 256

Acetazolamide

Acetazolamide in the treatment of abnormal oculovestibular response, 215

Acetylcholine

The effect of preoperative flurbiprofen on miosis produced by acetylcholine during cataract surgery, 735

Acquired immunodeficiency syndrome

Macular edema in acquired immunodeficiency syndrome-related microvasculopathy, 770

Rapidly progressive outer retinal necrosis in the acquired immunodeficiency syndrome (correspondence), 255

Albinism

Variable expression of albinism within a single kindred, 419

Amblyopia

Flotation devices to facilitate amblyopia therapy (letter), 110

The gradient filter test to assess amblyopia (correspondence), 119

Aminoglycoside

Conjunctival necrosis after administration of topical fortified aminoglycosides, 690

Amiodarone

Identification of amiodarone in corneal deposits (letter), 518

Anesthesia

Contralateral cavernous sinus syndrome after retrobulbar anesthetic injection (letter), 773

Anisocoria

Anisocoria in the pigmentary dispersion syndrome (correspondence), 384

Antibiotic drugs

An in vitro study of the potency and stability of fortified ophthalmic antibiotic preparations, 686

Aphakia

Epikeratoplasty with nonlyophilized tissue in children with aphakia, 407

Apraclonidine

Control of intraocular pressure with apraclonidine hydrochloride after cataract extraction, 184

Follicular conjunctivitis associated with apraclonidine (letter), 105

Palpebral fissure responses to topical adrenergic drugs, 706

Arrhythmia

The oculocardiac reflex during enucleation (letter), 378

Artery occlusion

Transesophageal echocardiography for detecting mitral valve prolapse with retinal artery occlusions (letter), 103

Use of transesophageal echocardiography for detection of a likely source of embolization to the central retinal artery (letter), 104

Vertebral artery occlusion complicating perimetry (letter), 516

Asteroid hyalosis

Prevalence and association of asteroid hyalosis with systemic diseases, 289

Astigmatism

Large refractive change after strabismus surgery (letter), 371

Automated perimetry

Automated perimetry in glaucoma, 235

B

Betaxolol

The effect of topical antiglaucoma drugs on the results of high-pass resolution perimetry, 711

Blepharitis

Role of cell-mediated immunity to staphylococci in blepharitis, 473

Blepharoptosis

Blepharoptosis caused by systemic thymoxamine (letter), 524

Epiphora caused by blepharoptosis (letter), 649

Blood-cell velocity

Blood-cell velocity in the nailfold capillaries of patients with normal-tension and high-tension glaucoma, 585

Books and Computer Software

Advances in Cataract Surgery, by Cangelosi, G. C. (ed.), 389

Age-Related Cataract, by Young, R. W., 527

Angle-Closure Glaucoma, by Hyams, S., 385

Atlas of Ophthalmic Surgery, by Jaffe, N. S., 385

The Best in Medical Humor, by Bennett, H. J., 781

Cataract Surgery. Alternative Small-Incision Techniques, by Rozakis, G. W. (ed.), 260

- Clinical Tests of Vision, by Frisén, L., 386
- Color Atlas of Ophthalmic Surgery. Strabismus, by Wright, K. W., 779
- Complications of Glaucoma Therapy, by Sherwood, M. B., and Spaeth, G. L., 389
- Cosmetic Blepharoplasty, by Bosniak, S. L., 778
- Current Concepts of Multifocal Intraocular Lenses, by Maxwell, A., and Nordan, L. T. (eds.), 389
- EndNote Plus, 780
- Eye Care in Developing Nations, ed. 2, by Schwab, L., 781
- Eye Diseases in Hot Climates, ed. 2, by Sandford-Smith, J., 259
- The Eye in Systemic Disease, ed. 2, by Kanski, J. J., and Thomas, D. J., 781
- Graves' Ophthalmopathy, by Wall, J. R., and How, J. (eds.), 781
- Handbook of Ocular Drug Therapy and Ocular Side Effects of Systemic Drugs, by Pavan-Langston, D., and Dunkel, E. C., 259
- The History of Ophthalmology, vol. 9. The First and Second Half of the Nineteenth Century, by Hirschberg, J., 779
- How to Write and Publish Papers in the Medical Sciences, ed. 2, by Huth, E. J. (ed.), 781
- Laser. Its Clinical Uses in Eye Diseases, ed. 2, by Constable, I. J., and Lim, A. S. M., 390
- Laser Surgery of the Posterior Segment, by Bloom, S. M., and Brucker, A. J., 388
- Lens Implant Power Calculation, ed. 3, by Retzlaff, J. A., Sanders, D. R., and Kraff, M., 388
- Les Strabismes. De l'analyse clinique à la synthèse chirurgicale, ed. 2, by Spielmann, A., 390
- Les Strabismes. Tome Premier. Les Divergences Oculaires, by Pigassou-Albouy, R., 782
- Manual of Visual Fields, by Werner, E. B. (ed.), 527
- The Molecular Biology of the Retina, by Farber, D. B., and Chader, G. J. (eds.), 390
- Normal Pressure Glaucomas, by Bechettille, A., 122
- Ophthalmic Echography. Ophthalmic Technical Skills Series, by Kendall, C. J., 390
- Ophthalmology Oral History Series. A Link With Our Past. An Interview With David Glendenning Cogan, M. D., by Hughes, S. S., 782
- Optics, Physiology and Vision, by McKee, S. P., and Nakayama, K. (eds.), 782
- Orthoptic Assessment and Management, by Stidwill, D., 660
- Phacoemulsification Surgery, by Devine, T. M., and Banko, W. (eds.), 782
- Practical Management of Squint, by Pittar, G., 527
- Ptois, ed. 4, by Callahan, M., and Beard, C., 778
- Radiology of the Eye and Orbit. Modern Neuroradiology, vol. 4, by Newton, T. H., and Bilaniuk, L. T. (eds.), 258
- Retinal and Choroidal Manifestations of Systemic Disease, by Singerman, L. J., and Jampol, L. M., 390
- Retinal Nerve Fiber Layer Photography, by Roloff, L. W., 387
- Small-incision Cataract Surgery, by Gills, J. P., and Sanders, D. R. (eds.), 390
- Style. Toward Clarity and Grace, by Williams, J. M., 389
- Textbook of Advanced Phacoemulsification Techniques, by Koch, P. S., and Davison, J. A. (eds.), 390
- Thyroid Eye Disease, ed. 2, by Char, D. H., 122
- Visual Allusions. Pictures of Perception, by Wade, N., 386
- Visual Fields. Examination and Interpretation, by Walsh, T. J. (ed.), 390
- Von Helmholtz-Augenspiegel zur Funduskamera, by Schett, A., 122
- Wally, The Scholarly Walrus, by Hill, L., 660
- Year Book of Ophthalmology 1990, by Laibson, P. R. (ed.), 123
- Borrelia sp.**
Retinal vasculitis with proliferative retinopathy in a patient with evidence of *Borrelia burgdorferi* infection (letter), 243
- C**
- Canaliculitis**
Retained Veirs rod and canaliculitis (letter), 251
- Candida sp.**
Candida albicans corneal ulcer associated with crack cocaine (letter), 248
Endogenous *Candida* species endophthalmitis associated with increased levels of D-arabinitol in serum and vitreous (letter), 379
- Capsulorhexis**
The elastic properties of the lens capsule in capsulorhexis, 628
Experimental nucleus extraction through a capsulorhexis in an eye with pseudoexfoliation syndrome (letter), 645
- Carcinoma**
Meibomian gland carcinoma in a 20-year-old patient (letter), 114
Metastatic renal cell carcinoma of the iris manifesting as an intrastromal iris cyst (letter), 113
- Carney complex**
The Carney complex with ocular signs suggestive of cardiac myxoma, 699

Cataract

- Comparison of a 3- and 6-mm incision in combined phacoemulsification and trabeculectomy, 189
- Contralateral cavernous sinus syndrome after retrobulbar anesthetic injection (letter), 773
- Control of intraocular pressure with apraclonidine hydrochloride after cataract extraction, 184
- Delayed-onset pseudophakic endophthalmitis, 163
- Delayed-onset pseudophakic endophthalmitis (correspondence), 656
- The effect of preoperative flurbiprofen on miosis produced by acetylcholine during cataract surgery, 735
- The elastic properties of the lens capsule in capsulorhexis, 628
- Extracapsular cataract extraction with intraocular lens implantation after scleral buckling surgery, 174
- Nd:YAG laser treatment for recurrent hyphemas in pseudophakia (letter), 513
- A new method for documenting lens opacities, 65
- Nuclear sclerotic cataract after vitrectomy for idiopathic epiretinal membranes causing macular pucker, 434
- Posterior chamber intraocular lens implantation in eyes with inactive and active proliferative diabetic retinopathy, 158
- Quantitative analysis of lens changes after vitrectomy by fluorophotometry, 179

Cefazolin

- An in vitro study of the potency and stability of fortified ophthalmic antibiotic preparations, 686

Central retinal vein

- The natural course of central retinal vein occlusion (correspondence), 525

Children

- Aberrant extraocular fibrous band as a cause of strabismus (letter), 370
- Bilateral congenital oculomotor nerve palsy in a child with brain anomalies, 555
- Disk neovascularization in chronic anterior uveitis (letter), 241
- Epikeratoplasty with nonlyophilized tissue in children with aphakia, 407
- The gradient filter test to assess amblyopia (correspondence), 119
- Large refractive change after strabismus surgery (letter), 371
- Leptomeningeal dissemination of optic pathway gliomas in three children, 719
- A population-based study of ocular abnormalities in premature children aged 5 to 10 years, 539

- The prevalence of retinal vascular abnormalities in children and adolescents with essential hypertension, 205

- Pseudophakic pupillary-block glaucoma in children, 715

- Scleritis and Wegener's granulomatosis in children, 430

- Unilateral manifestation of the Vogt-Koyanagi-Harada syndrome in a 7-year-old child (letter), 380

Choroid

- Histopathologic evidence of fibrovascular ingrowth four weeks after placement of the hydroxyapatite orbital implant, 363
- In vivo phosphorus 31 magnetic resonance spectroscopy of human uveal melanomas and other intraocular tumors, 276
- The management of retinal detachments associated with choroidal colobomas by vitreous surgery, 271
- Microwave thermotherapy for choroidal hemangioma (letter), 240
- Pneumocystis carinii* choroiditis after long-term aerosolized pentamidine therapy (correspondence), 118
- Vitrectomy retinotomy aspiration biopsy of choroidal tumors (correspondence), 121

Choroiditis

- Pneumocystis carinii* choroiditis after long-term aerosolized pentamidine therapy (correspondence), 118

Ciliary body

- Chronic ciliary pain secondary to posterior chamber intraocular lens loop incarceration (letter), 513

Cirrhosis

- Hepatic cirrhosis as a doubtful cause of eyelid retraction (letter), 109

***Clostridium* sp.**

- Clostridium perfringens* endophthalmitis (letter), 654

Cocaine

- Candida albicans* corneal ulcer associated with crack cocaine (letter), 248
- Palpebral fissure responses to topical adrenergic drugs, 706
- Urine drug screening for cocaine after lacrimal surgery, 703

***Cochliomyia* sp.**

- Nosocomial conjunctival ophthalmomyiasis with *Cochliomyia macellaria* (letter), 520

Coloboma

- The management of retinal detachments associated with choroidal colobomas by vitreous surgery, 271

Cone

- Relatively enhanced S cone function in the Goldmann-Favre syndrome, 446

Congenital disorders

Bilateral congenital oculomotor nerve palsy in a child with brain anomalies, 555

The Carney complex with ocular signs suggestive of cardiac myxoma, 699

The clinical characteristics of pedigrees of Leber's hereditary optic neuropathy with the 11778 mutation, 750

Early-onset autosomal dominant retinitis pigmentosa with severe hyperopia, 454

Hereditary hemorrhagic macular dystrophy, 294

Keratoconus and congenital hip dysplasia (letter), 775

A magnetic resonance imaging study of the upshoot-downshoot phenomenon of Duane's retraction syndrome, 548

Neuro-imaging and positron emission tomography of congenital homonymous hemianopsia, 413

Ocular findings in patients with autosomal dominant retinitis pigmentosa and rhodopsin, proline-347-leucine, 614

Ultrastructural study of Norrie's disease, 439

Variable expression of albinism within a single kindred, 419

Conjunctiva

Conjunctival necrosis after administration of topical fortified aminoglycosides, 690

Immunofluorescence findings in pseudopemphigoid induced by short-term idoxuridine administration (letter), 375

Isolated neurofibromas of the conjunctiva, 694

Tear cytology in conjunctival melanoma (letter), 648

Conjunctivitis

Follicular conjunctivitis associated with apraclonidine (letter), 105

Contact lens

Corneal ulcer and adverse reaction rates in premarket contact lens studies, 457; correction, 792

How safe are disposable soft contact lenses?, 766

Contrast sensitivity

Contrast sensitivity as an early indicator of acute mountain sickness (letter), 651

Loss of contrast sensitivity in cystic fibrosis, 427

Cornea

Candida albicans corneal ulcer associated with crack cocaine (letter), 248

Changes in corneal curvature at different excimer laser ablative depths (letter), 382

A comparison of penetrating keratoplasty to epikeratoplasty in the surgical management of keratoconus, 145

Corneal ulcer and adverse reaction rates in premarket contact lens studies, 457; correction, 792

The effect of allograft rejection after penetrating keratoplasty on central endothelial cell density, 739

The effects of Nd:YAG laser iridotomy on the corneal endothelium, 505

Epidemiologic characteristics, predisposing factors, and etiologic diagnosis of corneal ulceration in Nepal, 92

Herpes simplex dendritic keratitis after keratoplasty, 480

Human and monkey corneal endothelium expression of low-density lipoprotein receptors, 84

Identification of amiodarone in corneal deposits (letter), 518

Incidence of prominent corneal nerves in multiple endocrine neoplasia type 2A, 307

Infectious crystalline keratopathy after relaxing incisions (letter), 374

Paraproteinemic corneal deposits in plasma cell myeloma, 312

Peripheral ulcerative keratitis related to Lyme disease (letter), 244

Squamous cell carcinoma of the cornea, 571

Successful treatment of recurrent corneal erosion with Nd:YAG anterior stromal puncture (correspondence), 252

Terrien's marginal degeneration associated with vernal conjunctivitis (letter), 517

Corneoscleral limbus

Squamous cell carcinoma of the cornea, 571

Corrections

Corneal ulcer and adverse reaction rates in premarket contact lens studies, 457; correction, 792

Treatment of traumatic optic neuropathy with corticosteroids—correction (correspondence), 526

Corticosteroid

A new technique for the administration of intraoperative periocular corticosteroids (letter), 647

Treatment of traumatic optic neuropathy with corticosteroids—correction (correspondence), 526

Cyanoacrylate

Infectious keratitis and cyanoacrylate adhesive, 466

Cyclophotocoagulation

Malignant glaucoma after Nd:YAG cyclophotocoagulation (letter), 245

Cyst

Metastatic renal cell carcinoma of the iris manifesting as an intrastromal iris cyst (letter), 113

Cystic fibrosis

Loss of contrast sensitivity in cystic fibrosis, 427

D**Dacryocystitis**

Acute dacryocystitis after punctal occlusion for keratoconjunctivitis sicca (letter), 769

Dacryocystorhinostomy

Urine drug screening for cocaine after lacrimal surgery, 703

Diabetes

Bilateral endogenous endophthalmitis in a patient with diabetes and renal papillary necrosis (letter), 653

Prevalence and association of asteroid hyalosis with systemic diseases, 289

Visual field defects in diabetic patients with primary open-angle glaucoma, 581

Diabetic retinopathy

Posterior chamber intraocular lens implantation in eyes with inactive and active proliferative diabetic retinopathy, 158

Dipivefrin

Reversible lower eyelid ectropion associated with dipivefrin (letter), 650

Dry-eye syndrome

Acute dacryocystitis after punctal occlusion for keratoconjunctivitis sicca (letter), 769

The importance of the Schirmer test with nasal stimulation (letter), 106

Keratoconjunctivitis sicca caused by diphenoxylate hydrochloride with atropine sulfate (Lomotil) (letter), 377

Duane's retraction syndrome

A magnetic resonance imaging study of the upshoot-downshoot phenomenon of Duane's retraction syndrome, 548

Dysplasia

Keratoconus and congenital hip dysplasia (letter), 775

E**Echography**

Echographic diagnosis of dural carotid-cavernous sinus fistulas, 77

Transesophageal echocardiography for detecting mitral valve prolapse with retinal artery occlusions (letter), 103

Use of transesophageal echocardiography for detection of a likely source of embolization to the central retinal artery (letter), 104

Ectropion

Reversible lower eyelid ectropion associated with dipivefrin (letter), 650

Edema

Comparison of intraocular lens fixation techniques performed during penetrating keratoplasty, 743

Macular edema in acquired immunodeficiency syndrome-related microvasculopathy, 770

Editorials

Hydroxyamphetamine. A good drug lost? (BURDE, R. M., and THOMPSON, H. S.), 100

In defense of animal research (VON NOORDEN, G. K.), 367

A plea for low tech (KRAMER, S. G.), 508

Senile accommodative degeneration (SAD) (JAMPOLSKY, A.), 510

Endoillumination

Photic retinal injury from endoillumination during vitrectomy, 42

Endophthalmitis

Bilateral endogenous endophthalmitis in a patient with diabetes and renal papillary necrosis (letter), 653

Clostridium perfringens endophthalmitis (letter), 654

Delayed-onset pseudophakic endophthalmitis, 163

Delayed-onset pseudophakic endophthalmitis (correspondence), 656

Endogenous *Candida* species endophthalmitis associated with increased levels of D-arabinitol in serum and vitreous (letter), 379

Endothelium

The effect of allograft rejection after penetrating keratoplasty on central endothelial cell density, 739

The effects of Nd:YAG laser iridotomy on the corneal endothelium, 505

Human and monkey corneal endothelium expression of low-density lipoprotein receptors, 84

Enucleation

Histopathologic evidence of fibrovascular ingrowth four weeks after placement of the hydroxyapatite orbital implant, 363

The oculocardiac reflex during enucleation (letter), 378

Epikeratoplasty

A comparison of penetrating keratoplasty to epikeratoplasty in the surgical management of keratoconus, 145

Epikeratoplasty with nonlyophilized tissue in children with aphakia, 407

Epinephrine

The effect of topical antiglaucoma drugs on the results of high-pass resolution perimetry, 711

Epiphora

Epiphora caused by blepharoptosis (letter), 649

Epiretinal membrane

Nuclear sclerotic cataract after vitrectomy for idiopathic epiretinal membranes causing macular pucker, 434

Epitheliopathy

Retinal pigment epitheliopathy in acute leukemia (letter), 111

Epithelium

Mucogenic secondary open-angle glaucoma in diffuse epithelial ingrowth treated by block-excision, 230

Evisceration

A new instrument for use in evisceration (letter), 115

Eyelash

An eyelash nidus for dacryoliths of the lacrimal excretory and secretory systems, 624

Eyelid

Blepharoptosis caused by systemic thymoxamine (letter), 524

Discoid lupus erythematosus of the eyelid complicated by wound dehiscence (letter), 108

Epiphora caused by blepharoptosis (letter), 649

Eyelid tumors in the proteus syndrome (letter), 521

Hepatic cirrhosis as a doubtful cause of eyelid retraction (letter), 109

Meibomian gland carcinoma in a 20-year-old patient (letter), 114

Palpebral fissure responses to topical adrenergic drugs, 706

Reversible lower eyelid ectropion associated with dipivefrin (letter), 650

Surgical management of oculomotor nerve palsy, 71

Surgical management of oculomotor nerve palsy (correspondence), 658

F**Familial exudative vitreoretinopathy**

Signs, complications, and platelet aggregation in familial exudative vitreoretinopathy, 34

Fibrin

Intracameral tissue plasminogen activator for resolution of fibrin clots after glaucoma filtering procedures (letter), 247

Filtering surgery

Intracameral tissue plasminogen activator for resolution of fibrin clots after glaucoma filtering procedures (letter), 247

Fistula

Echographic diagnosis of dural carotid-cavernous sinus fistulas, 77

Transient cranial nerve palsies after cavernous sinus fistula embolization (letter), 771

Flavobacterium sp.

Flavobacterium meningosepticum keratitis successfully treated with topical trimethoprim-sulfamethoxazole (letter), 116

Flurbiprofen sodium

The effect of preoperative flurbiprofen on miosis produced by acetylcholine during cataract surgery, 735

Fovea

Surgical removal of subfoveal neovascularization in the presumed ocular histoplasmosis syndrome, 1

Frosted branch angiitis

Unilateral frosted branch angiitis, 682

Fuchs' heterochromic iridocyclitis

The epidemiologic association of Fuchs' heterochromic iridocyclitis and ocular toxoplasmosis, 356

G**Gammopathy**

Paraproteinemic corneal deposits in plasma cell myeloma, 312

Genetics

The clinical characteristics of pedigrees of Leber's hereditary optic neuropathy with the 11778 mutation, 750

Glaucoma

Automated perimetry in glaucoma, 235

Blood-cell velocity in the nailfold capillaries of patients with normal-tension and high-tension glaucoma, 585

Comparison of a 3- and 6-mm incision in combined phacoemulsification and trabeculectomy, 189

A comparison of total and partial tenonectomy with trabeculectomy, 323

Correlation between intraocular pressure control and progressive glaucomatous damage in primary open-angle glaucoma, 51

Correlation of the blind spot size to the area of the optic disk and parapapillary atrophy, 559

The effect of topical antiglaucoma drugs on the results of high-pass resolution perimetry, 711

The effects of Nd:YAG laser iridotomy on the corneal endothelium, 505

Follicular conjunctivitis associated with apraclonidine (letter), 105

Initial glaucomatous optic disk and retinal nerve fiber layer abnormalities and their progression, 485

Intracameral tissue plasminogen activator for resolution of fibrin clots after glaucoma filtering procedures (letter), 247

Intraocular pressure and the rate of visual field loss in chronic open-angle glaucoma, 491

In vitro videographic comparison of argon and Nd:YAG laser iridotomy, 589

- Malignant glaucoma after Nd:YAG cyclophotocoagulation (letter), 245
- Mucogenic secondary open-angle glaucoma in diffuse epithelial ingrowth treated by block-excision, 230
- Postoperative complications after Molteno implant surgery, 319
- Pseudophakic pupillary-block glaucoma in children, 715
- Reproducibility of topographic measurements of the normal and glaucomatous optic nerve head with the laser tomographic scanner, 221
- Reversible lower eyelid ectropion associated with dipivefrin (letter), 650
- Sector palsy of the sphincter pupillae muscle after argon laser trabeculoplasty (letter), 511
- Therapeutic ultrasound for the treatment of glaucoma, 327
- Visual field defects in diabetic patients with primary open-angle glaucoma, 581
- Glioma**
- Leptomeningeal dissemination of optic pathway gliomas in three children, 719
- Magnetic resonance imaging signs of optic nerve gliomas in neurofibromatosis 1, 729
- Goldmann-Favre syndrome**
- Relatively enhanced S cone function in the Goldmann-Favre syndrome, 446
- Graft**
- The effect of allograft rejection after penetrating keratoplasty on central endothelial cell density, 739
- Epikeratoplasty with nonlyophilized tissue in children with aphakia, 407
- Herpes simplex dendritic keratitis after keratoplasty, 480
- Repair of a giant scleral ulcer with a scleral graft and tissue glue (letter), 251
- Graves' ophthalmopathy**
- Hepatic cirrhosis as a doubtful cause of eyelid retraction (letter), 109
- Gyrate atrophy**
- Ocular clinicopathologic study of gyrate atrophy, 24

H

- Hemangioma**
- Microwave thermotherapy for choroidal hemangioma (letter), 240
- Hemianopsia**
- Neuro-imaging and positron emission tomography of congenital homonymous hemianopsia, 413
- Hemorrhage**
- Tissue plasminogen activator treatment of experimental subretinal hemorrhage, 197

Herpes simplex

- Herpes simplex dendritic keratitis after keratoplasty, 480

Herpesvirus

- Rapidly progressive outer retinal necrosis in the acquired immunodeficiency syndrome (correspondence), 255

Hydroxyamphetamine

- Hydroxyamphetamine. A good drug lost? (editorial), 100
- Palpebral fissure responses to topical adrenergic drugs, 706

Hyperopia

- Early-onset autosomal dominant retinitis pigmentosa with severe hyperopia, 454

Hypertension

- The prevalence of retinal vascular abnormalities in children and adolescents with essential hypertension, 205

Hyphema

- Nd:YAG laser treatment for recurrent hyphemas in pseudophakia (letter), 513

I

Ichthyosis

- Ichthyosis and crystalline maculopathy (letter), 522

Idoxuridine

- Immunofluorescence findings in pseudopemphigoid induced by short-term idoxuridine administration (letter), 375

Intraocular lens

- Chronic ciliary pain secondary to posterior chamber intraocular lens loop incarceration (letter), 513
- Comparison of a 3- and 6-mm incision in combined phacoemulsification and trabeculectomy, 189
- Comparison of intraocular lens fixation techniques performed during penetrating keratoplasty, 743
- Delayed-onset pseudophakic endophthalmitis, 163
- Delayed-onset pseudophakic endophthalmitis (correspondence), 656
- Experimental nucleus extraction through a capsulorhexis in an eye with pseudoexfoliation syndrome (letter), 645
- Extracapsular cataract extraction with intraocular lens implantation after scleral buckling surgery, 174
- Posterior chamber intraocular lens implantation in eyes with inactive and active proliferative diabetic retinopathy, 158
- Pseudophakic pupillary-block glaucoma in children, 715

Intraocular pressure

Control of intraocular pressure with apraclonidine hydrochloride after cataract extraction, 184

Correlation between intraocular pressure control and progressive glaucomatous damage in primary open-angle glaucoma, 51

The effect of Perkins, Tono-Pen, and Schiötz tonometry on intraocular pressure, 59

Increased intraocular pressure in severely burned patients, 56

Increased intraocular pressure in severely burned patients (correspondence), 657

Intraocular pressure and the rate of visual field loss in chronic open-angle glaucoma, 491

Postoperative complications after Molteno implant surgery, 319

Iridectomy

Identification, prevention, and treatment of silicone oil pupillary block after an inferior iridectomy, 501

Iridocyclitis

The epidemiologic association of Fuchs' heterochromic iridocyclitis and ocular toxoplasmosis, 356

Iridotomy

The effects of Nd:YAG laser iridotomy on the corneal endothelium, 505

In vitro videographic comparison of argon and Nd:YAG laser iridotomy, 589

Iris

Flexible iris retractor, 776

Hereditary hemorrhagic macular dystrophy, 294

The influence of iris pigmentation on the miotic effect of thymoxamine, 351

Metastatic renal cell carcinoma of the iris manifesting as an intrastromal iris cyst (letter), 113

A physical analysis of the factors that determine the contour of the iris, 338

The physiologic characteristics of relative pupillary block, 344

Ischemia

The natural course of central retinal vein occlusion (correspondence), 525

Optic nerve sheath decompression for the treatment of progressive nonarteritic ischemic optic neuropathy, 724

K**Keratitis**

Conjunctival necrosis after administration of topical fortified aminoglycosides, 690

Epidemiologic characteristics, predisposing factors, and etiologic diagnosis of corneal ulceration in Nepal, 92

Flavobacterium meningosepticum keratitis successfully treated with topical trimethoprim-sulfamethoxazole (letter), 116

Herpes simplex dendritic keratitis after keratoplasty, 480

Infectious keratitis and cyanoacrylate adhesive, 466

Peripheral ulcerative keratitis related to Lyme disease (letter), 244

Role of cell-mediated immunity to staphylococci in blepharitis, 473

Successful medical management of *Acanthamoeba* keratitis (correspondence), 256

Varicella disciform stromal keratitis, 575

Keratoconjunctivitis sicca

Acute dacryocystitis after punctal occlusion for keratoconjunctivitis sicca (letter), 769

Keratoconjunctivitis sicca caused by diphenoxylate hydrochloride with atropine sulfate (Lomotil) (letter), 377

Keratoconus

A comparison of penetrating keratoplasty to epikeratoplasty in the surgical management of keratoconus, 145

The effect of allograft rejection after penetrating keratoplasty on central endothelial cell density, 739

Keratoconus and congenital hip dysplasia (letter), 775

Keratopathy

Infectious crystalline keratopathy after relaxing incisions (letter), 374

Keratoplasty

Herpes simplex dendritic keratitis after keratoplasty, 480

Ketoprofen

Ketoprofen in the treatment of scleritis (letter), 249

***Klebsiella* sp.**

Bilateral endogenous endophthalmitis in a patient with diabetes and renal papillary necrosis (letter), 653

L**Lacrimal apparatus**

Acute dacryocystitis after punctal occlusion for keratoconjunctivitis sicca (letter), 769

Endoscopic laser-assisted lacrimal surgery, 152

An eyelash nidus for dacryoliths of the lacrimal excretory and secretory systems, 624

Lacrimal gland epidermal growth factor production and the ocular surface, 763

Retained Veirs rod and canaliculitis (letter), 251

- Urine drug screening for cocaine after lacrimal surgery, 703
- Laser**
- Changes in corneal curvature at different excimer laser ablative depths (letter), 382
 - The effects of Nd:YAG laser iridotomy on the corneal endothelium, 505
 - Endoscopic laser-assisted lacrimal surgery, 152
 - Hereditary hemorrhagic macular dystrophy, 294
 - In vitro videographic comparison of argon and Nd:YAG laser iridotomy, 589
 - Malignant glaucoma after Nd:YAG cyclophotocoagulation (letter), 245
 - Nd:YAG laser treatment for recurrent hyphemas in pseudophakia (letter), 513
 - Reproducibility of topographic measurements of the normal and glaucomatous optic nerve head with the laser tomographic scanner, 221
 - Sector palsy of the sphincter pupillae muscle after argon laser trabeculoplasty (letter), 511
 - Successful treatment of recurrent corneal erosion with Nd:YAG anterior stromal puncture (correspondence), 252
- Lattice degeneration**
- Prevalence of lattice degeneration and its relation to axial length in severe myopia, 20
- Leber's optic atrophy**
- The clinical characteristics of pedigrees of Leber's hereditary optic neuropathy with the 11778 mutation, 750
- Lens**
- The elastic properties of the lens capsule in capsulorhexis, 628
 - Experimental nucleus extraction through a capsulorhexis in an eye with pseudoexfoliation syndrome (letter), 645
 - A new method for documenting lens opacities, 65
 - Nuclear sclerotic cataract after vitrectomy for idiopathic epiretinal membranes causing macular pucker, 434
 - Quantitative analysis of lens changes after vitrectomy by fluorophotometry, 179
- Leukemia**
- Retinal pigment epitheliopathy in acute leukemia (letter), 111
- Lipoprotein**
- Human and monkey corneal endothelium expression of low-density lipoprotein receptors, 84
- Lomotil**
- Keratoconjunctivitis sicca caused by diphenoxylate hydrochloride with atropine sulfate (Lomotil) (letter), 377
- Lupus erythematosus**
- Discoid lupus erythematosus of the eyelid complicated by wound dehiscence (letter), 108
- Lyme borreliosis**
- Peripheral ulcerative keratitis related to Lyme disease (letter), 244
 - Retinal vasculitis with proliferative retinopathy in a patient with evidence of *Borrelia burgdorferi* infection (letter), 243
- M**
- Macula**
- Hereditary hemorrhagic macular dystrophy, 294
 - Macular edema in acquired immunodeficiency syndrome-related microvasculopathy, 770
 - Nuclear sclerotic cataract after vitrectomy for idiopathic epiretinal membranes causing macular pucker, 434
 - Recognition and removal of the posterior cortical vitreous during vitreoretinal surgery for impending macular hole, 611
- Macular dystrophy**
- Hereditary hemorrhagic macular dystrophy, 294
- Maculopathy**
- Ichthyosis and crystalline maculopathy (letter), 522
- Magnetic resonance imaging**
- Magnetic resonance imaging evaluation of uveal tumors, 633
 - Magnetic resonance imaging signs of optic nerve gliomas in neurofibromatosis 1, 729
- Medical education**
- Assessment of ophthalmic training programs, 642
- Meetings, Conferences, Symposia**
- Ocular Microbiology and Immunology Group—24th Annual Meeting (O'DAY, D. M.), 391
- Meibomian gland**
- Meibomian gland carcinoma in a 20-year-old patient (letter), 114
- Melanoma**
- Histopathologic evidence of fibrovascular ingrowth four weeks after placement of the hydroxyapatite orbital implant, 363
 - In vivo phosphorus 31 magnetic resonance spectroscopy of human uveal melanomas and other intraocular tumors, 276
 - Magnetic resonance imaging evaluation of uveal tumors, 633
 - Tear cytology in conjunctival melanoma (letter), 648

Miosis

The effect of preoperative flurbiprofen on miosis produced by acetylcholine during cataract surgery, 735

The influence of iris pigmentation on the miotic effect of thymoxamine, 351

Mitral valve prolapse

Transesophageal echocardiography for detecting mitral valve prolapse with retinal artery occlusions (letter), 103

Use of transesophageal echocardiography for detection of a likely source of embolization to the central retinal artery (letter), 104

Molteno glaucoma implant

Postoperative complications after Molteno implant surgery, 319

Mountain sickness

Contrast sensitivity as an early indicator of acute mountain sickness (letter), 651

Multiple endocrine neoplasia

Incidence of prominent corneal nerves in multiple endocrine neoplasia type 2A, 307

Muscle

Aberrant extraocular fibrous band as a cause of strabismus (letter), 370

A simple transposition procedure for complicated strabismus, 302

Mydriasis

The influence of iris pigmentation on the miotic effect of thymoxamine, 351

Myeloma

Paraproteinemic corneal deposits in plasma cell myeloma, 312

Myopia

Prevalence of lattice degeneration and its relation to axial length in severe myopia, 20

Scleral buckling for rhegmatogenous retinal detachment associated with severe myopia, 595

Stability of refraction during four years after radial keratotomy in the Prospective Evaluation of Radial Keratotomy Study, 133

Myxoma

The Carney complex with ocular signs suggestive of cardiac myxoma, 699

N**Necrosis**

Bilateral endogenous endophthalmitis in a patient with diabetes and renal papillary necrosis (letter), 653

Conjunctival necrosis after administration of topical fortified aminoglycosides, 690

Neovascularization

Disk neovascularization in chronic anterior uveitis (letter), 241

Surgical removal of subfoveal neovascularization in the presumed ocular histoplasmosis syndrome, 1

Neurofibromatosis

Isolated neurofibromas of the conjunctiva, 694

Magnetic resonance imaging signs of optic nerve gliomas in neurofibromatosis 1, 729

Norrie's disease

Ultrastructural study of Norrie's disease, 439

Nystagmus

Variable expression of albinism within a single kindred, 419

O**Obituaries**

Dobbie, J. Graham 1926-1990 (FETKENHOUR, C.), 394

Michels, Ronald G. 1943-1991 (RYAN, S. J.), 661

Occlusion

Flotation devices to facilitate amblyopia therapy (letter), 110

Oculomotor nerve

Bilateral congenital oculomotor nerve palsy in a child with brain anomalies, 555

Late recovery of function after oculomotor nerve palsy, 566

Surgical management of oculomotor nerve palsy, 71

Surgical management of oculomotor nerve palsy (correspondence), 658

Oculovestibular response

Acetazolamide in the treatment of abnormal oculovestibular response, 215

Open-angle glaucoma

Correlation between intraocular pressure control and progressive glaucomatous damage in primary open-angle glaucoma, 51

Intraocular pressure and the rate of visual field loss in chronic open-angle glaucoma, 491

Visual field defects in diabetic patients with primary open-angle glaucoma, 581

Ophthalmomyiasis

Nosocomial conjunctival ophthalmomyiasis with *Cochliomyia macellaria* (letter), 520

Optic disk

Correlation of the blind spot size to the area of the optic disk and parapapillary atrophy, 559

Disk neovascularization in chronic anterior uveitis (letter), 241

Initial glaucomatous optic disk and retinal nerve fiber layer abnormalities and their progression, 485

Optic nerve

Magnetic resonance imaging signs of optic nerve gliomas in neurofibromatosis 1, 729

The oculocardiac reflex during enucleation (letter), 378

Optic nerve sheath decompression for the treatment of progressive nonarteritic ischemic optic neuropathy, 724

Reproducibility of topographic measurements of the normal and glaucomatous optic nerve head with the laser tomographic scanner, 221

Treatment of traumatic optic neuropathy with corticosteroids—correction (correspondence), 526

Optic neuritis

Visual recovery in patients with optic neuritis and visual loss to no light perception, 209

Optic neuropathy

Optic nerve sheath decompression for the treatment of progressive nonarteritic ischemic optic neuropathy, 724

Treatment of traumatic optic neuropathy with corticosteroids—correction (correspondence), 526

Orbit

Histopathologic evidence of fibrovascular ingrowth four weeks after placement of the hydroxyapatite orbital implant, 363

Magnetic resonance imaging signs of optic nerve gliomas in neurofibromatosis 1, 729

P

Palsy

Bilateral congenital oculomotor nerve palsy in a child with brain anomalies, 555

Late recovery of function after oculomotor nerve palsy, 566

Sector palsy of the sphincter pupillae muscle after argon laser trabeculoplasty (letter), 511

Surgical management of oculomotor nerve palsy, 71

Surgical management of oculomotor nerve palsy (correspondence), 658

Transient cranial nerve palsies after cavernous sinus fistula embolization (letter), 771

Penetrating keratoplasty

Comparison of intraocular lens fixation techniques performed during penetrating keratoplasty, 743

A comparison of penetrating keratoplasty to epikeratoplasty in the surgical management of keratoconus, 145

The effect of allograft rejection after penetrating keratoplasty on central endothelial cell density, 739

Infectious crystalline keratopathy after relaxing incisions (letter), 374

Pentamidine

Pneumocystis carinii choroiditis after long-term aerosolized pentamidine therapy (correspondence), 118

Perimetry

The effect of topical antiglaucoma drugs on the results of high-pass resolution perimetry, 711

Vertebral artery occlusion complicating perimetry (letter), 516

Perspectives

Assessment of ophthalmic training programs, 642

Automated perimetry in glaucoma, 235

How safe are disposable soft contact lenses?, 766

Lacrimal gland epidermal growth factor production and the ocular surface, 763

Phacoemulsification

Comparison of a 3- and 6-mm incision in combined phacoemulsification and trabeculectomy, 189

Phenylephrine

Palpebral fissure responses to topical adrenergic drugs, 706

Photocoagulation

Hereditary hemorrhagic macular dystrophy, 294

Pigment dispersion syndrome

Anisocoria in the pigmentary dispersion syndrome (correspondence), 384

Pilocarpine

The effect of topical antiglaucoma drugs on the results of high-pass resolution perimetry, 711

Pneumocystis sp.

Pneumocystis carinii choroiditis after long-term aerosolized pentamidine therapy (correspondence), 118

Presumed ocular histoplasmosis syndrome

Surgical removal of subfoveal neovascularization in the presumed ocular histoplasmosis syndrome, 1

Proliferative vitreoretinopathy

Causes of failure after initial vitreoretinal surgery for severe proliferative vitreoretinopathy, 8

Causes of failure after repeat vitreoretinal surgery for recurrent proliferative vitreoretinopathy, 15

Proteus syndrome

Eyelid tumors in the proteus syndrome (letter), 521

Pseudoexfoliation syndrome

Experimental nucleus extraction through a capsulorhexis in an eye with pseudoexfoliation syndrome (letter), 645

Pseudopemphigoid

Immunofluorescence findings in pseudopemphigoid induced by short-term idoxuridine administration (letter), 375

Pseudophakia

Nd:YAG laser treatment for recurrent hyphemas in pseudophakia (letter), 513

Pupil

Anisocoria in the pigmentary dispersion syndrome (correspondence), 384

Bilateral congenital oculomotor nerve palsy in a child with brain anomalies, 555

The effect of preoperative flurbiprofen on miosis produced by acetylcholine during cataract surgery, 735

Flexible iris retractor, 776

Hydroxyamphetamine. A good drug lost? (editorial), 100

Identification, prevention, and treatment of silicone oil pupillary block after an inferior iridectomy, 501

A physical analysis of the factors that determine the contour of the iris, 338

The physiologic characteristics of relative pupillary block, 344

Sector palsy of the sphincter pupillae muscle after argon laser trabeculoplasty (letter), 511

Pupillary block

Identification, prevention, and treatment of silicone oil pupillary block after an inferior iridectomy, 501

A physical analysis of the factors that determine the contour of the iris, 338

The physiologic characteristics of relative pupillary block, 344

Pseudophakic pupillary-block glaucoma in children, 715

R

Radial keratotomy

Stability of refraction during four years after radial keratotomy in the Prospective Evaluation of Radial Keratotomy Study, 133

Rectus muscle

A magnetic resonance imaging study of the upshoot-downshoot phenomenon of Duane's retraction syndrome, 548

Refraction

Large refractive change after strabismus surgery (letter), 371

Stability of refraction during four years after radial keratotomy in the Prospective Evaluation of Radial Keratotomy Study, 133

Retina

Acute multifocal inner retinitis, 673

Causes of failure after initial vitreoretinal surgery for severe proliferative vitreoretinopathy, 8

Causes of failure after repeat vitreoretinal surgery for recurrent proliferative vitreoretinopathy, 15

Initial glaucomatous optic disk and retinal nerve fiber layer abnormalities and their progression, 485

Light damage in detached retina, 47

Loss of contrast sensitivity in cystic fibrosis, 427

Macular edema in acquired immunodeficiency syndrome-related microvasculopathy, 770

The natural course of central retinal vein occlusion (correspondence), 525

Ocular clinicopathologic study of gyrate atrophy, 24

Photoc retinal injury from endoillumination during vitrectomy, 42

Prevalence of lattice degeneration and its relation to axial length in severe myopia, 20

The prevalence of retinal vascular abnormalities in children and adolescents with essential hypertension, 205

Rapidly progressive outer retinal necrosis in the acquired immunodeficiency syndrome (correspondence), 255

Recognition and removal of the posterior cortical vitreous during vitreoretinal surgery for impending macular hole, 611

Relatively enhanced S cone function in the Goldmann-Favre syndrome, 446

Retinal vasculitis with proliferative retinopathy in a patient with evidence of *Borrelia burgdorferi* infection (letter), 243

Signs, complications, and platelet aggregation in familial exudative vitreoretinopathy, 34

Surgical removal of subfoveal neovascularization in the presumed ocular histoplasmosis syndrome, 1

Tissue plasminogen activator treatment of experimental subretinal hemorrhage, 197

Transesophageal echocardiography for detecting mitral valve prolapse with retinal artery occlusions (letter), 103

Ultrastructural study of Norrie's disease, 439

Unilateral frosted branch angiitis, 682

Use of transesophageal echocardiography for detection of a likely source of embolization to the central retinal artery (letter), 104

Retinal detachment

Causes of failure after initial vitreoretinal surgery for severe proliferative vitreoretinopathy, 8

Causes of failure after repeat vitreoretinal surgery for recurrent proliferative vitreoretinopathy, 15

Light damage in detached retina, 47

The management of retinal detachments associated with choroidal colobomas by vitreous surgery, 271

Prevalence of lattice degeneration and its relation to axial length in severe myopia, 20

Scleral buckling for rhegmatogenous retinal detachment associated with severe myopia, 595

Retinal necrosis

Rapidly progressive outer retinal necrosis in the acquired immunodeficiency syndrome (correspondence), 255

Retinal pigment epithelium

Hereditary hemorrhagic macular dystrophy, 294

Retinal pigment epitheliopathy in acute leukemia (letter), 111

Retinitis

Acute multifocal inner retinitis, 673

Rapidly progressive outer retinal necrosis in the acquired immunodeficiency syndrome (correspondence), 255

Retinitis pigmentosa

Early-onset autosomal dominant retinitis pigmentosa with severe hyperopia, 454

Ocular findings in patients with autosomal dominant retinitis pigmentosa and rhodopsin, proline-347-leucine, 614

Retinopathy

The prevalence of retinal vascular abnormalities in children and adolescents with essential hypertension, 205

Retinal vasculitis with proliferative retinopathy in a patient with evidence of *Borrelia burgdorferi* infection (letter), 243

Retinopathy in human vitamin E deficiency, 774

Retinotomy

Vitreotomy retinotomy aspiration biopsy of choroidal tumors (correspondence), 121

Rod

Relatively enhanced S cone function in the Goldmann-Favre syndrome, 446

S

Schirmer test

The importance of the Schirmer test with nasal stimulation (letter), 106

Schwannoma

The Carney complex with ocular signs suggestive of cardiac myxoma, 699

Sclera

Ketoprofen in the treatment of scleritis (letter), 249

Repair of a giant scleral ulcer with a scleral graft and tissue glue (letter), 251

Scleral buckle

Extracapsular cataract extraction with intraocular lens implantation after scleral buckling surgery, 174

Scleral buckling for rhegmatogenous retinal detachment associated with severe myopia, 595

Scleritis

Ketoprofen in the treatment of scleritis (letter), 249

Scleritis and Wegener's granulomatosis in children, 430

Sclerosis

Nuclear sclerotic cataract after vitrectomy for idiopathic epiretinal membranes causing macular pucker, 434

Silicone oil

Identification, prevention, and treatment of silicone oil pupillary block after an inferior iridectomy, 501

Spectroscopy

In vivo phosphorus 31 magnetic resonance spectroscopy of human uveal melanomas and other intraocular tumors, 276

Squamous cell carcinoma

Squamous cell carcinoma of the cornea, 571

Staphylococcus sp.

Role of cell-mediated immunity to staphylococci in blepharitis, 473

Strabismus

Aberrant extraocular fibrous band as a cause of strabismus (letter), 370

Large refractive change after strabismus surgery (letter), 371

A simple transposition procedure for complicated strabismus, 302

Stroma

Varicella disciform stromal keratitis, 575

T

Tears

Lacrimal gland epidermal growth factor production and the ocular surface, 763

Tear cytology in conjunctival melanoma (letter), 648

Tenonectomy

A comparison of total and partial tenonectomy with trabeculectomy, 323

Terrien's disease

Terrien's marginal degeneration associated with vernal conjunctivitis (letter), 517

Thymoxamine

Blepharoptosis caused by systemic thymoxamine (letter), 524

The influence of iris pigmentation on the miotic effect of thymoxamine, 351

Timolol

The effect of topical antiglaucoma drugs on the results of high-pass resolution perimetry, 711

Tissue plasminogen activator

Intracameral tissue plasminogen activator for resolution of fibrin clots after glaucoma filtering procedures (letter), 247

Tissue plasminogen activator treatment of experimental subretinal hemorrhage, 197

Tobramycin

An in vitro study of the potency and stability of fortified ophthalmic antibiotic preparations, 686

Tonometry

The effect of Perkins, Tono-Pen, and Schiötz tonometry on intraocular pressure, 59

Toxoplasma sp.

Current practices in the management of ocular toxoplasmosis, 601

The epidemiologic association of Fuchs' heterochromic iridocyclitis and ocular toxoplasmosis, 356

Toxoplasmosis

Current practices in the management of ocular toxoplasmosis, 601

The epidemiologic association of Fuchs' heterochromic iridocyclitis and ocular toxoplasmosis, 356

Trabeculectomy

Comparison of a 3- and 6-mm incision in combined phacoemulsification and trabeculectomy, 189

A comparison of total and partial tenonectomy with trabeculectomy, 323

Trabeculoplasty

Sector palsy of the sphincter pupillae muscle after argon laser trabeculoplasty (letter), 511

Trimethoprim-sulfamethoxazole

Flavobacterium meningosepticum keratitis successfully treated with topical trimethoprim-sulfamethoxazole (letter), 116

Tumor

Eyelid tumors in the proteus syndrome (letter), 521

Histopathologic evidence of fibrovascular ingrowth four weeks after placement of the hydroxyapatite orbital implant, 363

In vivo phosphorus 31 magnetic resonance spectroscopy of human uveal melanomas and other intraocular tumors, 276

Leptomeningeal dissemination of optic pathway gliomas in three children, 719

Magnetic resonance imaging evaluation of uveal tumors, 633

Metastatic renal cell carcinoma of the iris manifesting as an intrastromal iris cyst (letter), 113

Microwave thermotherapy for choroidal hemangioma (letter), 240

Squamous cell carcinoma of the cornea, 571

Vitrectomy retinotomy aspiration biopsy of choroidal tumors (correspondence), 121

U**Ulcer**

Epidemiologic characteristics, predisposing factors, and etiologic diagnosis of corneal ulceration in Nepal, 92

Ultrasound

Therapeutic ultrasound for the treatment of glaucoma, 327

Uvea

In vivo phosphorus 31 magnetic resonance spectroscopy of human uveal melanomas and other intraocular tumors, 276

Magnetic resonance imaging evaluation of uveal tumors, 633

Uveitis

Current practices in the management of ocular toxoplasmosis, 601

Disk neovascularization in chronic anterior uveitis (letter), 241

Recurrent uveitis preceded by swelling of skin tattoos (letter), 515

V**Varicella**

Varicella disciform stromal keratitis, 575

Vasculitis

Retinal vasculitis with proliferative retinopathy in a patient with evidence of *Borrelia burgdorferi* infection (letter), 243

Vein occlusion

The natural course of central retinal vein occlusion (correspondence), 525

Vernal conjunctivitis

Terrien's marginal degeneration associated with vernal conjunctivitis (letter), 517

Vertigo

Acetazolamide in the treatment of abnormal oculovestibular response, 215

Visual acuity

The gradient filter test to assess amblyopia (correspondence), 119

Mean visual acuity (letter), 372

Visual field

Intraocular pressure and the rate of visual field loss in chronic open-angle glaucoma, 491

Visual field defects in diabetic patients with primary open-angle glaucoma, 581

Visual loss

Visual recovery in patients with optic neuritis and visual loss to no light perception, 209

Vitamin

Loss of contrast sensitivity in cystic fibrosis, 427

Retinopathy in human vitamin E deficiency, 774

Vitrectomy

Causes of failure after initial vitreoretinal surgery for severe proliferative vitreoretinopathy, 8

Causes of failure after repeat vitreoretinal surgery for recurrent proliferative vitreoretinopathy, 15

The management of retinal detachments associated with choroidal colobomas by vitreous surgery, 271

Nuclear sclerotic cataract after vitrectomy for idiopathic epiretinal membranes causing macular pucker, 434

Photic retinal injury from endoillumination during vitrectomy, 42

Quantitative analysis of lens changes after vitrectomy by fluorophotometry, 179

Recognition and removal of the posterior cortical vitreous during vitreoretinal surgery for impending macular hole, 611

Vitrectomy retinotomy aspiration biopsy of choroidal tumors (correspondence), 121

Vitreous

The management of retinal detachments associated with choroidal colobomas by vitreous surgery, 271

Nuclear sclerotic cataract after vitrectomy for idiopathic epiretinal membranes causing macular pucker, 434

Recognition and removal of the posterior cortical vitreous during vitreoretinal surgery for impending macular hole, 611

Vogt-Koyanagi-Harada syndrome

Unilateral manifestation of the Vogt-Koyanagi-Harada syndrome in a 7-year-old child (letter), 380

W**Wegener's granulomatosis**

Scleritis and Wegener's granulomatosis in children, 430

AUTHOR INDEX

A

- AABERG, T. M.: See BROOCKER, G., 642
 AABERG, T. M.: See LEWIS, H., 8, 15
 ABRAMS, G. W.: See LEWIS, H., 8
 ADAMSONS, I., TAYLOR, K. I., ENGER, C., and TAYLOR, H. R.: A new method for documenting lens opacities, 65
 AIRAKSINEN, P. J.: See TUULONEN, A., 485
 ALAVI, A.: See BOSLEY, T. M., 413
 ALPER, M. G.: Radiology of the Eye and Orbit. Modern Neuroradiology, vol. 4, by Newton, T. H., and Bilaniuk, L. T. (eds.) (book review), 258
 ALWARD, W. L. M.: EndNote Plus (book review), 780
 ANDERSON, D. R., JIN, J. C., and WRIGHT, M. M.: The physiologic characteristics of relative pupillary block, 344
 ANGRA, S. K.: See VAJPAYEE, R. B., 715
 APPLE, D. J.: See ASSIA, E. I., 628, 645
 APPLE, D. J.: See LEGLER, U. F. C., 513
 ARFFA, R. C.: See PORTNOY, S. L., 113
 ARMESTO, D. M., LEE, A. M., PRAGER, T. C., GOOSEY, C. B., and GOOSEY, J. D.: Epikeratoplasty with nonlyophilized tissue in children with aphakia, 407
 ASHKENAZI, I.: See BARTOV, E., 501
 ASSIA, E. I., APPLE, D. J., TSAI, J. C., and LIM, E. S.: The elastic properties of the lens capsule in capsulorhexis, 628
 ASSIA, E. I., HOGGATT, J. P., and APPLE, D. J.: Experimental nucleus extraction through a capsulorhexis in an eye with pseudoexfoliation syndrome (letter), 645
 AVIEL, E.: See KREMER, I., 375

B

- BAEK, N. H.: See ZEITER, J. H., 581
 BALDINGER, J.: See WU, G., 294
 BARATZ, K. H., BARTLEY, G. B., CAMPBELL, R. J., and GARRITY, J. A.: An eyelash nidus for dacryoliths of the lacrimal excretory and secretory systems, 624
 BARISHAK, Y. R.: See SPIERER, A., 370
 BARKOVICH, A. J.: See GOOD, W. V., 555
 BARTLEY, G. B.: Reversible lower eyelid ectropion associated with dipivefrin (letter), 650
 BARTLEY, G. B., and GORMAN, C. A.: Hepatic cirrhosis as a doubtful cause of eyelid retraction (letter), 109
 BARTLEY, G. B.: See BARATZ, K. H., 624
 BARTLEY, G. B.: See KALINA, P. H., 694
 BARTOV, E., HUNA, R., ASHKENAZI, I., MELAMED, S., GUTMAN, I., NAVEH, N., and TREISTER, G.: Identification, prevention, and treatment of silicone oil pupillary block after an inferior iridectomy, 501
 BECKER, B. B.: Retained Veirs rod and canaliculitis (letter), 251
 BERGER, A. S., TYCHSEN, L., and ROSENBLUM, J. L.: Retinopathy in human vitamin E deficiency, 774
 BERGER, S. T., MONDINO, B. J., HOFT, R. H., and FARLEY, M. K.: Reply to DRIEBE, W. T., JR., and STERN, G. A.: Successful medical management of *Acanthamoeba* keratitis (correspondence), 257
 BERGREN, R. L., BROWN, G. C., and DUKER, J. S.: Prevalence and association of asteroid hyalosis with systemic diseases, 289
 BERSON, E. L., ROSNER, B., SANDBERG, M. A., WEIGEL-DIFRANCO, C., and DRYJA, T. P.: Ocular findings in patients with autosomal dominant retinitis pigmentosa and rhodopsin, proline-347-leucine, 614
 BEST, D.: See DAVIS, R. M., 743
 BHALLA, J. S., VASHISHT, S., GUPTA, V. K., and SEN, A. K.: Meibomian gland carcinoma in a 20-year-old patient (letter), 114
 BIRD, E. F.: See GOOSEY, J. D., 145
 BLASINI, M.: See MILLER, K. N., 323
 BLEIN, J.-P.: See NORDMANN, J.-P., 651
 BLITSTEIN, B.: See SABATES, F. N., JR., 771
 BLONDEAU, P.: Normal Pressure Glaucomas, by Béchetoille, A. (book review), 122
 BLOOM, J. N., GRAVISS, E. R., and MARDELLI, P. G.: A magnetic resonance imaging study of the upshoot-downshoot phenomenon of Duane's retraction syndrome, 548
 BLUMENTHAL, M.: See MELAMED, S., 319
 BOS, P. J. M.: See VERBRAAK, F. D., 111
 BOSLEY, T. M., KIYOSAWA, M., MOSTER, M., HARBOUR, R., ZIMMERMAN, R., SAVINO, P. J., SERGOTT, R. C., ALAVI, A., and REIVICH, M.: Neuro-imaging and positron emission tomography of congenital homonymous hemianopsia, 413
 BOWE, B. E., SNYDER, J. W., and EIFERMAN, R. A.: An in vitro study of the potency and stability of fortified ophthalmic antibiotic preparations, 686
 BRANCATO, R.: See NUCCI, P., 775
 BREMER, D. L.: See LEGUIRE, L. E., 427

- BROOCKER, G., and AABERG, T. M.: Assessment of ophthalmic training programs, 642
- BROWN, G. C.: See BERGREN, R. L., 289
- BROWN, J. D.: See HARDTEN, D. R., 245
- BRUGGERS, C. S., FRIEDMAN, H. S., PHILLIPS, P. C., WIENER, M. D., HOCKENBERGER, B., OAKES, W. J., and BUCKLEY, E. G.: Leptomenigeal dissemination of optic pathway gliomas in three children, 719
- BRYAN, L. E.: See UPADHYAY, M. P., 92
- BUCCI, F. A., JR., and HOLLAND, E. J.: *Flavobacterium meningosepticum* keratitis successfully treated with topical trimethoprim-sulfamethoxazole (letter), 116
- BUCKLEY, E. G., and TOWNSHEND, L. M.: A simple transposition procedure for complicated strabismus, 302
- BUCKLEY, E. G.: See BRUGGERS, C. S., 719
- BUETTNER, H.: See KALINA, P. H., 694
- BURDE, R. M., and THOMPSON, H. S.: Hydroxyamphetamine. A good drug lost? (editorial), 100
- BURKE, M. J.: See DANIELS, S. R., 205
- C**
- CAHANE, M.: See MELAMED, S., 319
- CAMERON, J. A., and HIDAYAT, A. A.: Squamous cell carcinoma of the cornea, 571
- CAMERON, J. D.: See MEIUSI, R. S., 108
- CAMPBELL, R. J.: See BARATZ, K. H., 624
- CAMPBELL, R. J.: See KALINA, P. H., 694
- CAPRIOLI, J.: Automated perimetry in glaucoma, 235
- CARNEY, J. A.: See KENNEDY, R. H., 699
- CARTER, K. D.: See MUNDEN, P. M., 378, 706
- CASTRONUOVO, S., SIMON, J. W., KANDEL, G. L., MORIER, A., WOLF, B., WITKOP, C. J., and JENKINS, P. L.: Variable expression of albinism within a single kindred, 419
- CATALANO, R. A.: See GOTTLÖB, I., 71, 658
- CAVANAUGH, T. B., and GOTTSCH, J. D.: Infectious keratitis and cyanoacrylate adhesive, 466
- CELORIO, J. M., and PRUETT, R. C.: Prevalence of lattice degeneration and its relation to axial length in severe myopia, 20
- CHABBRA, V. K.: See VAJPAYEE, R. B., 715
- CHAN, C.-C.: See MANSOUR, A. M., 515
- CHANDLER, D. B.: See PRUM, B. E., JR., 589
- CHAR, D. H.: See RAYMOND, W. R., IV, 633
- CHEN, M. T.: See LIN, C. P., 251
- CHENG, K. P.: See SLAMOVITS, T. L., 209
- CHERFAN, G. M., MICHELS, R. G., DE BUSTROS, S., ENGER, C., and GLASER, B. M.: Nuclear sclerotic cataract after vitrectomy for idiopathic epiretinal membranes causing macular pucker, 434
- CHESS, Q.: See FASTENBERG, D. M., 121
- CHITKARA, D. K., and HUDSON, J. M.: Blepharoptosis caused by systemic thymoxamine (letter), 524
- CHODOSH, J., CLARRIDGE, J. E., and MATOBA, A.: Nosocomial conjunctival ophthalmomyiasis with *Cochliomyia macellaria* (letter), 520
- CHONG, L. P.: See DUGEL, P. U., 118
- CHRISTENSEN, R. E.: See PANEK, W. C., 505
- CLARRIDGE, J. E.: See CHODOSH, J., 520
- COHEN, E.: See MACRAE, S. M., 792
- COLEMAN, D. J.: See SILVERMAN, R. H., 327
- CORNICELLI, J. A.: See ELNER, S. G., 84
- CRAWFORD, S. E.: See SACKS, R. D., 430
- CRUZ, O. A., PATRINELY, J. R., REYNA, G. S., and KING, J. W.: Urine drug screening for cocaine after lacrimal surgery, 703
- CULBERTSON, W.: See WARING, G. O., III, 133
- D**
- DANIELS, S. R., LIPMAN, M. J., BURKE, M. J., and LOGGIE, J. M. H.: The prevalence of retinal vascular abnormalities in children and adolescents with essential hypertension, 205
- DART, J. K. G.: See DAVISON, C. R., 690
- DAVIS, H. R.: See ELNER, S. G., 84
- DAVIS, R. M., BEST, D., and GILBERT, G. E.: Comparison of intraocular lens fixation techniques performed during penetrating keratoplasty, 743
- DAVISON, C. R., TUFT, S. J., and DART, J. K. G.: Conjunctival necrosis after administration of topical fortified aminoglycosides, 690
- DE BUSTROS, S.: See CHERFAN, G. M., 434
- DE JUAN, E., JR., and HICKINGBOTHAM, D.: Flexible iris retractor, 776
- DE JUAN, E., JR.: See ENYEDI, L. B., 439
- DE JUAN, E., JR.: See HANNEKEN, A., 271
- DE KEYSER, J., HERROELEN, L., and VAN LANGENHOVE, L.: Vertebral artery occlusion complicating perimetry (letter), 516
- DELUISE, V. P., and O'LEARY, M. J.: Peripheral ulcerative keratitis related to Lyme disease (letter), 244
- DENIS, P.: See NORDMANN, J.-P., 651
- DENISON, C. E.: See MUNDEN, P. M., 706
- DE POTTER, P., VON WEYMARN, C., and ZOGRAFOS, L.: In vivo phosphorus 31 magnetic resonance spectroscopy of human uveal melanomas and other intraocular tumors, 276
- DE POTTER, P.: See SHIELDS, C. L., 363
- DESATNIK, H.: See SPIERER, A., 370
- DIEHL, D. L. C., ROBIN, A. L., and WAND, M.: The influence of iris pigmentation on the mitotic effect of thymoxamine, 351
- DONZIS, D. M.: See MEDWAY, D. C., 249
- DONZIS, P. B.: See MEDWAY, D. C., 249
- DOYLE, J. W.: See SUGIN, S. L., 682

- DREHER, A. W., TSO, P. C., and WEINREB, R. N.: Reproducibility of topographic measurements of the normal and glaucomatous optic nerve head with the laser tomographic scanner, 221
- DRIEBE, W. T., JR., and STERN, G. A.: Successful medical management of *Acanthamoeba* keratitis (correspondence), 256
- DRYJA, T. P.: See BERSON, E. L., 614
- DUGEL, P. U., RAO, N. A., FORSTER, D. J., CHONG, L. P., FRANGIEH, G. T., SATTler, F., and LO-PRESTI, J. A.: Reply to TEICH, S. A., ROSENBLATT, M., and FRIEDMAN, A.: *Pneumocystis carinii* choroiditis after long-term aerosolized pentamidine therapy (correspondence), 118
- DUGEL, P. U.: See FORSTER, D. J., 256
- DUKER, J. S., and SHAKIN, E. P.: Rapidly progressive outer retinal necrosis in the acquired immunodeficiency syndrome (correspondence), 255
- DUKER, J. S.: See BERGREN, R. L., 289
- DUTTON, J. J.: Ptoxis, ed. 4, by Callahan, M., and Beard, C. (book review), 778

E

- EAGLE, R. C., JR.: See KENNEDY, R. H., 699
- EAGLE, R. C., JR.: See SHIELDS, C. L., 363
- EGAN, D.: See MACRAE, S. M., 792
- EIFERMAN, R. A.: See BOWE, B. E., 686
- ELNER, S. G., ELNER, V. M., PAVILACK, M. A., DAVIS, H. R., CORNICELLI, J. A., and YUE, B. Y. J. T.: Human and monkey corneal endothelium expression of low-density lipoprotein receptors, 84
- ELNER, V. M.: See ELNER, S. G., 84
- EMIG, M.: See WHITACRE, M. M., 59
- ENGEL, C.: See ADAMSONS, I., 65
- ENGEL, C.: See CHERFAN, G. M., 434
- ENGSTROM, R. E., JR., HOLLAND, G. N., NUSSENBLATT, R. B., and JABS, D. A.: Current practices in the management of ocular toxoplasmosis, 601
- ENYEDI, L. B., DE JUAN, E., JR., and GAITAN, A.: Ultrastructural study of Norrie's disease, 439
- EPSTEIN, A. D.: See PEARSON, P. A., 773
- ERNEST, J. T.: See TRIPATHI, R. C., 247
- EVANS, L. S.: Increased intraocular pressure in severely burned patients, 56
- EVANS, L. S.: Reply to NEUHAUS, R. W.: Increased intraocular pressure in severely burned patients (correspondence), 658

F

- FARLEY, M. K.: See BERGER, S. T., 257
- FARRIS, B. K.: See HESTER, R. B., III, 215
- FASTENBERG, D. M., FINGER, P. T., CHESS, Q., PACKER, S., and KOIZUMI, J. H.: Reply to PEYMAN, G. A.: Vitrectomy retinotomy aspiration biopsy of choroidal tumors (correspondence), 121

- FERNÁNDEZ, M. C.: See JONAS, J. B., 559
- FETKENHOUR, C.: Dobbie, J. Graham 1926-1990 (obituary), 394
- FICKER, L., RAMAKRISHNAN, M., SEAL, D., and WRIGHT, P.: Role of cell-mediated immunity to staphylococci in blepharitis, 473
- FINGER, P. T., PAGLIONE, R. W., and PACKER, S.: Microwave thermotherapy for choroidal hemangioma (letter), 240
- FINGER, P. T.: See FASTENBERG, D. M., 121
- FISHER, J. C.: See GONNERING, R. S., 152
- FITZGERALD-SHELTON, K.: See MUSCH, D. C., 739
- FLAMMER, J.: See GASSER, P., 585
- FLANAGAN, J. C.: See KENNEDY, R. H., 699
- FLANNERY, J. G.: See LEWIS, H., 197
- FLYNN, H. W., JR.: See FOX, G. M., 163, 656
- FLYNN, H. W., JR.: See MEIN, C. E., 611
- FORSTER, D. J., DUGEL, P. U., FRANGIEH, G. T., LIGGETT, P. E., and RAO, N. A.: Reply to DUKER, J. S., and SHAKIN, E. P.: Rapidly progressive outer retinal necrosis in the acquired immunodeficiency syndrome (correspondence), 256
- FORSTER, D. J., GREEN, R. L., and RAO, N. A.: Unilateral manifestation of the Vogt-Koyanagi-Harada syndrome in a 7-year-old child (letter), 380
- FORSTER, D. J.: See DUGEL, P. U., 118
- FOSTER, R. E., GUTMAN, F. A., MEYERS, S. M., and LOWDER, C. Y.: Acute multifocal inner retinitis, 673
- FOURAKER, B. D.: See KINCAID, M. C., 374
- FOX, G. M., JOONDEPH, B. C., FLYNN, H. W., JR., PFLUGFELDER, S. C., and ROUSSEL, T. J.: Delayed-onset pseudophakic endophthalmitis, 163
- FOX, G. M., JOONDEPH, B. C., FLYNN, H. W., JR., PFLUGFELDER, S. C., and ROUSSEL, T. J.: Reply to HAIMANN, M. H., WEISS, H., AND MILLER, J. A.: Delayed-onset pseudophakic endophthalmitis (correspondence), 656
- FRANGIEH, G. T.: See DUGEL, P. U., 118
- FRANGIEH, G. T.: See FORSTER, D. J., 256
- FRIEDMAN, A. H.: See HAUG, S. J., 518
- FRIEDMAN, A. H.: See TEICH, S. A., 118
- FRIEDMAN, H. S.: See BRUGGERS, C. S., 719
- FRIEDMAN, S. M.: See SUGIN, S. L., 682
- FRISHBERG, B.: See PALESTINE, A. G., 770

G

- GAITAN, A.: See ENYEDI, L. B., 439
- GALLO, J. E., and LENNERSTRAND, G.: A population-based study of ocular abnormalities in premature children aged 5 to 10 years, 539
- GARRITY, J. A.: See BARATZ, K. H., 624
- GARRITY, J. A.: See PACH, J. M., 241

GASS, J. D. M.: See JACOBSON, S. G., 446

GASSER, P., and FLAMMER, J.: Blood-cell velocity in the nailfold capillaries of patients with normal-tension and high-tension glaucoma, 585

GEGGEL, H. S.: Reply to RUBINFELD, R. S., MACRAE, S. M., and LAIBSON, P. R.: Successful treatment of recurrent corneal erosion with Nd:YAG anterior stromal puncture (correspondence), 254

GEISSE, L. J.: Nd:YAG laser treatment for recurrent hyphemas in pseudophakia (letter), 513

GILBERT, G. E.: See DAVIS, R. M., 743

GLASER, B. M.: See CHERFAN, G. M., 434

GLATT, H. J.: Acute dacryocystitis after punctal occlusion for keratoconjunctivitis sicca (letter), 769

GLATT, H. J.: Epiphora caused by blepharoptosis (letter), 649

GOLDBERG, R. A.: See HAVUNJIAN, R. H., 653

GOLNIK, K. C., and MILLER, N. R.: Late recovery of function after oculomotor nerve palsy, 566

GONNERING, R. S., LYON, D. B., and FISHER, J. C.: Endoscopic laser-assisted lacrimal surgery, 152

GOOD, W. V., BARKOVICH, A. J., NICKEL, B. L., and HOYT, C. S.: Bilateral congenital oculomotor nerve palsy in a child with brain anomalies, 555

GOOSEY, C. B.: See ARMESTO, D. M., 407

GOOSEY, C. B.: See GOOSEY, J. D., 145

GOOSEY, J. D., PRAGER, T. C., GOOSEY, C. B., BIRD, E. F., and SANDERSON, J. C.: A comparison of penetrating keratoplasty to epikeratoplasty in the surgical management of keratoconus, 145

GOOSEY, J. D.: See ARMESTO, D. M., 407

GORMAN, C. A.: See BARTLEY, G. B., 109

GOTTLOB, I., CATALANO, R. A., and REINECKE, R. D.: Surgical management of oculomotor nerve palsy, 71

GOTTLOB, I., REINECKE, R. D., and CATALANO, R. A.: Reply to SAUNDERS, R. A., and ROGERS, G. L.: Surgical management of oculomotor nerve palsy (correspondence), 658

GOTTSCH, J. D.: See CAVANAUGH, T. B., 466

GRAVES, A.: See MARTIN-BOGLIND, L. M., 711

GRAVISS, E. R.: See BLOOM, J. N., 548

GREEN, R. L.: See FORSTER, D. J., 380

GREEN, W. R.: See WILSON, D. J., 24

GREENWALD, M. J.: See REYNOLDS, R. D., 371

GREENWALD, M. J.: See SACKS, R. D., 430

GREVEN, C. M., WEAVER, R. G., HARRIS, W. R., WATTS, L. E., and SLUSHER, M. M.: Trans-esophageal echocardiography for detecting mitral valve prolapse with retinal artery occlusions (letter), 103

GUPTA, V. K.: See BHALLA, J. S., 114

GUSEK, G. C.: See JONAS, J. B., 559

GUTMAN, F. A.: See FOSTER, R. E., 673

GUTMAN, I.: See BARTOV, E., 501

GUTMAN, I.: See MELAMED, S., 319

H

HACKER, H. D., and O'HARA, M.: Flotation devices to facilitate amblyopia therapy (letter), 110

HAIMANN, M. H., WEISS, H., and MILLER, J. A.: Delayed-onset pseudophakic endophthalmitis (correspondence), 656

HAMILL, M. B.: See WILHELMUS, K. R., 575

HANNEKEN, A., DE JUAN, E., JR., and MCCUEN, B. W., II: The management of retinal detachments associated with choroidal colobomas by vitreous surgery, 271

HANSEN, L. L., and WIEK, J.: The natural course of central retinal vein occlusion (correspondence), 525

HARBOUR, R.: See BOSLEY, T. M., 413

HARDTEN, D. R., and BROWN, J. D.: Malignant glaucoma after Nd:YAG cyclophotocoagulation (letter), 245

HARRIS, W. R.: See GREVEN, C. M., 103

HART, W. M., JR.: Manual of Visual Fields, by Werner, E. B. (ed.) (book review), 527

HARTEL, W. C.: See SPOOR, T. C., 526

HASSANEIN, K.: See WHITACRE, M. M., 59

HAUG, S. J., and FRIEDMAN, A. H.: Identification of amiodarone in corneal deposits (letter), 518

HAVUNJIAN, R. H., GOLDBERG, R. A., and HEPLER, R. S.: Bilateral endogenous endophthalmitis in a patient with diabetes and renal papillary necrosis (letter), 653

HAYASAKA, S., NODA, S., and SETOGAWA, T.: Endogenous *Candida* species endophthalmitis associated with increased levels of D-arabinitol in serum and vitreous (letter), 379

HENDERLY, D. E.: See SUGIN, S. L., 682

HEPLER, R. S.: See HAVUNJIAN, R. H., 653

HERMAN, C.: See MACRAE, S. M., 792

HERMAN, D. C.: See PACH, J. M., 241

HERROELEN, L.: See DE KEYSER, J., 516

HERSH, P. S.: See ZAGELBAUM, B. M., 248

HESTER, R. B., III, and FARRIS, B. K.: Acetazolamide in the treatment of abnormal oculovestibular response, 215

HICKINGBOTHAM, D.: See DE JUAN, E., JR., 776

HICKINGBOTHAM, D.: See PRUM, B. E., JR., 589

HIDAYAT, A. A.: See CAMERON, J. A., 571

HIROSE, T.: See WU, G., 294

HO, C.-H.: See MILLER, K. N., 323

HOCKENBERGER, B.: See BRUGGERS, C. S., 719

- HOFT, R. H.: See BERGER, S. T., 257
 HOGGATT, J. P.: See ASSIA, E. I., 645
 HOLLADAY, J. T., and PRAGER, T. C.: Mean visual acuity (letter), 372
 HOLLAND, E. J.: See BUCCI, F. A., JR., 116
 HOLLAND, E. J.: See MEIUSI, R. S., 108
 HOLLAND, G. N.: See ENGSTROM, R. E., JR., 601
 HOLLSTEN, D. A.: See WHITE, W. L., 115
 HOLMES, J. M., and JAY, W. M.: The effect of preoperative flurbiprofen on miosis produced by acetylcholine during cataract surgery, 735
 HOYT, C. S.: See GOOD, W. V., 555
 HOYT, W. F.: See IMES, R. K., 729
 HUANG, W. L.: See LIN, C. P., 251
 HUDSON, J. M.: See CHITKARA, D. K., 524
 HUNA, R.: See BARTOV, E., 501
 HUND, P.: See LEGLER, U. F. C., 513

I

- IDE, C. H.: See WILES, S. B., 184, 654
 IKEDA, M.: See KINOSHITA, S., 307
 IMES, R. K., and HOYT, W. F.: Magnetic resonance imaging signs of optic nerve gliomas in neurofibromatosis 1, 729
 ISHIGOOKA, H.: See OGURA, Y., 179

J

- JABS, D. A.: See ENGSTROM, R. E., JR., 601
 JACOBSON, S. G., ROMÁN, A. J., ROMÁN, M. I., GASS, J. D. M., and PARKER, J. A.: Relatively enhanced S cone function in the Goldmann-Favre syndrome, 446
 JAMPOL, L. M.: See SUGIN, S. L., 682
 JAMPOLSKY, A.: Senile accommodative degeneration (SAD) (editorial), 510
 JAY, W. M.: See HOLMES, J. M., 735
 JENKINS, P. L.: See CASTRONUOVO, S., 419
 JIN, J. C.: See ANDERSON, D. R., 344
 JIN, J. C.: See LYLE, W. A., 189
 JOHN, T.: How safe are disposable soft contact lenses?, 766
 JOHNSON, B. L.: See PORTNOY, S. L., 113
 JONAS, J. B., GUSEK, G. C., and FERNÁNDEZ, M. C.: Correlation of the blind spot size to the area of the optic disk and parapapillary atrophy, 559
 JONES, D. B.: See WILHELMUS, K. R., 575
 JOONDEPH, B. C.: A new technique for the administration of intraoperative periocular corticosteroids (letter), 647
 JOONDEPH, B. C.: See FOX, G. M., 163, 656
 JUDISCH, G. F.: See LAM, B. L., 454

K

- KACHMER, M. L.: See LEGUIRE, L. E., 427
 KAISERLING, E.: See STEUHL, K.-P., 312

- KALINA, P. H., BARTLEY, G. B., CAMPBELL, R. J., and BUETTNER, H.: Isolated neurofibromas of the conjunctiva, 694

- KALINA, P. H.: See PACH, J. M., 241

- KANDEL, G. L.: See CASTRONUOVO, S., 419

- KAPLAN, H. J.: See THOMAS, M. A., 1

- KARDON, R. H.: See MUNDEN, P. M., 706

- KARMACHARYA, P. C. D.: See UPADHYAY, M. P., 92

- KEECH, R. V.: Color Atlas of Ophthalmic Surgery. Strabismus, by Wright, K. W. (book review), 779

- KEECH, R. V., and KUTSCHKE, P. J.: Reply to NARDI, M.: The gradient filter test to assess amblyopia (correspondence), 120

- KENNEDY, R. H., FLANAGAN, J. C., EAGLE, R. C., JR., and CARNEY, J. A.: The Carney complex with ocular signs suggestive of cardiac myxoma, 699

- KINCAID, M. C., FOURAKER, B. D., and SCHANZLIN, D. J.: Infectious crystalline keratopathy after relaxing incisions (letter), 374

- KING, J. W.: See CRUZ, O. A., 703

- KINOSHITA, S., TANAKA, F., OHASHI, Y., IKEDA, M., and TAKAI, S.: Incidence of prominent corneal nerves in multiple endocrine neoplasia type 2A, 307

- KIRKCONNELL, W. S.: See LEGLER, U. F. C., 513

- KIYOSAWA, M.: See BOSLEY, T. M., 413

- KNORR, M.: See STEUHL, K.-P., 312

- KOIRALA, S.: See UPADHYAY, M. P., 92

- KOIZUMI, J. H.: See FASTENBERG, D. M., 121

- KOLDER, H. E.: Cataract Surgery. Alternative Small-Incision Techniques, by Rozakis, G. W. (ed.) (book review), 260

- KOLDER, H. E.: Lens Implant Power Calculation, ed. 3, by Retzlaff, J. A., Sanders, D. R., and Kraff, M. (book review), 388

- KOMMERELL, G.: See PFEIFFER, N., 511

- KRAMER, S. G.: A plea for low tech (editorial), 508

- KREIGER, A. E.: See RODRIGUEZ, F. J., 595

- KREMER, I.: Terrien's marginal degeneration associated with vernal conjunctivitis (letter), 517

- KREMER, I., ROZENBAUM, D., and AVIEL, E.: Immunofluorescence findings in pseudopemphigoid induced by short-term idoxuridine administration (letter), 375

- KÜCHLE, M., and NAUMANN, G. O. H.: Mucogenic secondary open-angle glaucoma in diffuse epithelial ingrowth treated by block-excision, 230

- KUHN, F., MORRIS, R., and MASSEY, M.: Photoc retinal injury from endoillumination during vitrectomy, 42

KUTNER, M. H.: See WARING, G. O., III, 133

KUTSCHKE, P. J.: See KEECH, R. V., 120

L

LAIBSON, P. R.: See RUBINFELD, R. S., 252

LAIBSON, P. R.: See WARING, G. O., III, 133

LAM, B. L., and JUDISCH, G. F.: Early-onset autosomal dominant retinitis pigmentosa with severe hyperopia, 454

LANG, G. E., SCHÖNHERR, U., and NAUMANN, G. O. H.: Retinal vasculitis with proliferative retinopathy in a patient with evidence of *Borrelia burgdorferi* infection (letter), 243

LEE, A. M.: See ARMESTO, D. M., 407

LEE, D. A.: See PANEK, W. C., 505

LEGLER, U. F. C., APPLE, D. J., HUND, P., and KIRK-CONNELL, W. S.: Chronic ciliary pain secondary to posterior chamber intraocular lens loop incarceration (letter), 513

LEGUIRE, L. E., PAPPA, K. S., KACHMER, M. L., ROGERS, G. L., and BREMER, D. L.: Loss of contrast sensitivity in cystic fibrosis, 427

LEHMAN, E.: See TRIPATHI, R. C., 247

LENNERSTRAND, G.: See GALLO, J. E., 539

LENSINK, D. B.: See SPOOR, T. C., 526

LESSNER, A., and MARGO, C. E.: Eyelid tumors in the proteus syndrome (letter), 521

LEWIS, H., and AABERG, T. M.: Causes of failure after repeat vitreoretinal surgery for recurrent proliferative vitreoretinopathy, 15

LEWIS, H., AABERG, T. M., and ABRAMS, G. W.: Causes of failure after initial vitreoretinal surgery for severe proliferative vitreoretinopathy, 8

LEWIS, H., RESNICK, S. C., FLANNERY, J. G., and STRAATSMA, B. R.: Tissue plasminogen activator treatment of experimental subretinal hemorrhage, 197

LEWIS, H.: See RODRIGUEZ, F. J., 595

LEWIS, R. A.: See WILKERSON, M., 105

LIGGETT, P. E.: See FORSTER, D. J., 256

LIM, E. S.: See ASSIA, E. I., 628

LIN, C. P., WU, Y. H., CHEN, M. T., and HUANG, W. L.: Repair of a giant scleral ulcer with a scleral graft and tissue glue (letter), 251

LINDSTROM, R. D.: See WARING, G. O., III, 133

LIPMAN, M. J.: See DANIELS, S. R., 205

LIPPMAN, R.: See MACRAE, S. M., 792

LISCH, W.: See STEUHL, K.-P., 312

LITWIN, K. L., MOREIRA, H., OHADI, C., and McDONNELL, P. J.: Changes in corneal curvature at different excimer laser ablative depths (letter), 382

LOGGIE, J. M. H.: See DANIELS, S. R., 205

LOPRESTI, J. A.: See DUGEL, P. U., 118

LOTT, M. T.: See NEWMAN, N. J., 750

LOWDER, C. Y.: See FOSTER, R. E., 673

LYLE, W. A., and JIN, J. C.: Comparison of a 3- and 6-mm incision in combined phacoemulsification and trabeculectomy, 189

LYNN, M. J.: See WARING, G. O., III, 133

LYON, D. B.: See GONNERING, R. S., 152

M

MACHEMER, R.: See ZILIS, J. D., 47

MACKENZIE, D.: See WILES, S. B., 184

MACRAE, S. M., HERMAN, C., STULTING, R. D., LIPPMAN, R., WHIPPLE, D., COHEN, E., EGAN, D., WILKINSON, C. P., SCOTT, C., SMITH, R. E., and PHILLIPS, D.: Corneal ulcer and adverse reaction rates in premarket contact lens studies, 457; correction, 792

MACRAE, S. M.: See RUBINFELD, R. S., 252

MADER, T. H., and STULTING, R. D.: Keratoconjunctivitis sicca caused by diphenoxylate hydrochloride with atropine sulfate (Lomotil) (letter), 377

MANNIS, M. J.: Atlas of Ophthalmic Surgery, by Jaffe, N. S. (book review), 385

MANNIS, M. J., PLOTNIK, R. D., SCHWAB, I. R., and NEWTON, R. D.: Herpes simplex dendritic keratitis after keratoplasty, 480

MANSOUR, A. M., and CHAN, C.-C.: Recurrent uveitis preceded by swelling of skin tattoos (letter), 515

MAO, L. K., STEWART, W. C., and SHIELDS, M. B.: Correlation between intraocular pressure control and progressive glaucomatous damage in primary open-angle glaucoma, 51

MARDELLI, P. G.: See BLOOM, J. N., 548

MARGO, C. E.: See LESSNER, A., 521

MARTIN, T. J.: Handbook of Ocular Drug Therapy and Ocular Side Effects of Systemic Drugs, by Pavan-Langston, D., and Dunkel, E. C. (book review), 259

MARTIN-BOGLIND, L. M., GRAVES, A., and WANGER, P.: The effect of topical antiglaucoma drugs on the results of high-pass resolution perimetry, 711

MASSEY, M.: See KUHN, F., 42

MATOKA, A.: See CHODOSH, J., 520

MCCUEN, B. W., II: See HANNEKEN, A., 271

MCDONALD, M. B.: See WARING, G. O., III, 133

MCDONNELL, P. J.: See LITWIN, K. L., 382

MEDWAY, D. C., DONZIS, D. M., and DONZIS, P. B.: Ketoprofen in the treatment of scleritis (letter), 249

- MEIN, C. E., and FLYNN, H. W., JR.: Recognition and removal of the posterior cortical vitreous during vitreoretinal surgery for impending macular hole, 611
- MEIUSI, R. S., CAMERON, J. D., HOLLAND, E. J., and SUMMERS, C. G.: Discoid lupus erythematosus of the eyelid complicated by wound dehiscence (letter), 108
- MELAMED, S., CAHANE, M., GUTMAN, I., and BLUMENTHAL, M.: Postoperative complications after Molteno implant surgery, 319
- MELAMED, S.: See BARTOV, E., 501
- MEYER, R. F.: See MUSCH, D. C., 739
- MEYERS, S. M.: See FOSTER, R. E., 673
- MICHELS, R. G.: See CHERFAN, G. M., 434
- MILLER, J. A.: See HAIMANN, M. H., 656
- MILLER, K. N., BLASINI, M., SHIELDS, M. B., and HO, C.-H.: A comparison of total and partial tenonectomy with trabeculectomy, 323
- MILLER, N. R.: See GOLNIK, K. C., 566
- MONDINO, B. J.: See BERGER, S. T., 257
- MOREIRA, H.: See LITWIN, K. L., 382
- MORIER, A.: See CASTRONUOVO, S., 419
- MORRIS, R.: See KUHN, F., 42
- MOSTER, M.: See BOSLEY, T. M., 413
- MUNDEN, P. M., CARTER, K. D., and NERAD, J. A.: The oculocardiac reflex during enucleation (letter), 378
- MUNDEN, P. M., KARDON, R. H., DENISON, C. E., and CARTER, K. D.: Palpebral fissure responses to topical adrenergic drugs, 706
- MUSCH, D. C., SCHWARTZ, A. E., FITZGERALD-SHELTON, K., SUGAR, A., and MEYER, R. F.: The effect of allograft rejection after penetrating keratoplasty on central endothelial cell density, 739
- MYERS, W. D.: See WARING, G. O., III, 133

N

- NARDI, M.: The gradient filter test to assess amblyopia (correspondence), 119
- NAUMANN, G. O. H.: See KÜCHLE, M., 230
- NAUMANN, G. O. H.: See LANG, G. E., 243
- NAVEH, N.: See BARTOV, E., 501
- NELSON, L. B.: See REYNOLDS, R. D., 371
- NERAD, J. A.: See MUNDEN, P. M., 378
- NEUHAUS, R. W.: Increased intraocular pressure in severely burned patients (correspondence), 657
- NEWELL, F. W.: The History of Ophthalmology, vol. 9. The First and Second Half of the Nineteenth Century, by Hirschberg, J. (book review), 779
- NEWELL, F. W.: Style. Toward Clarity and Grace, by Williams, J. M. (book review), 389
- NEWMAN, N. J., LOTT, M. T., and WALLACE, D. C.: The clinical characteristics of pedigrees of Leber's hereditary optic neuropathy with the 11778 mutation, 750

- NEWMAN, N. M.: Retinal Nerve Fiber Layer Photography, by Roloff, L. W. (book review), 387
- NEWTON, R. D.: See MANNIS, M. J., 480
- NICKEL, B. L.: See GOOD, W. V., 555
- NODA, S.: See HAYASAKA, S., 379
- NORDMANN, J.-P., RONCIN, J.-P., DENIS, P., BLEIN, J.-P., and SARAUX, H.: Contrast sensitivity as an early indicator of acute mountain sickness (letter), 651
- NORMAN, D.: See RAYMOND, W. R., IV, 633
- NUCCI, P., and BRANCATO, R.: Keratoconus and congenital hip dysplasia (letter), 775
- NUSSENBLATT, R. B.: See ENGSTROM, R. E., JR., 601

O

- OAKES, W. J.: See BRUGGERS, C. S., 719
- O'BRIEN, C., SCHWARTZ, B., TAKAMOTO, T., and WU, D. C.: Intraocular pressure and the rate of visual field loss in chronic open-angle glaucoma, 491
- OBSTBAUM, S. A.: See WARING, G. O., III, 133
- O'DAY, D. M.: Ocular Microbiology and Immunology Group—24th Annual Meeting, 391
- OGINO, N.: See OGURA, Y., 179
- O'GRADY, R. B.: See SACKS, R. D., 430
- OGURA, Y., TAKANASHI, T., ISHIGOOKA, H., and OGINO, N.: Quantitative analysis of lens changes after vitrectomy by fluorophotometry, 179
- OHADI, C.: See LITWIN, K. L., 382
- O'HARA, M.: See HACKER, H. D., 110
- OHASHI, Y.: See KINOSHITA, S., 307
- O'LEARY, M. J.: See DELUISE, V. P., 244

P

- PACH, J. M., HERMAN, D. C., GARRITY, J. A., and KALINA, P. H.: Disk neovascularization in chronic anterior uveitis (letter), 241
- PACKER, S.: See FASTENBERG, D. M., 121
- PACKER, S.: See FINGER, P. T., 240
- PAGLIONE, R. W.: See FINGER, P. T., 240
- PALESTINE, A. G., and FRISHBERG, B.: Macular edema in acquired immunodeficiency syndrome-related microvasculopathy, 770
- PANEK, W. C., LEE, D. A., and CHRISTENSEN, R. E.: The effects of Nd:YAG laser iridotomy on the corneal endothelium, 505
- PAPPA, K. S.: See LEGUIRE, L. E., 427
- PARK, J. K.: See TRIPATHI, R. C., 247
- PARKER, J. A.: See JACOBSON, S. G., 446
- PATIPA, M.: Cosmetic Blepharoplasty, by Bosniak, S. L. (book review), 778
- PATRINELY, J. R.: See CRUZ, O. A., 703
- PAVILACK, M. A.: See ELNER, S. G., 84
- PEARSON, P. A., SOLOMON, K. D., SMITH, T. J., and EPSTEIN, A. D.: Contralateral cavernous sinus syndrome after retrobulbar anesthetic injection (letter), 773

- PEARSON, W. N.: See WIZNIA, R. A., 104
 PERELL, H.: Angle-Closure Glaucoma, by Hyams, S. (book review), 385
 PERUSSE, P.: See WEISS, J. S., 648
 PEYMAN, G. A.: Vitrectomy retinotomy aspiration biopsy of choroidal tumors (correspondence), 121
 PFEIFFER, N., and KOMMERELL, G.: Sector palsy of the sphincter pupillae muscle after argon laser trabeculoplasty (letter), 511
 PFLUGFELDER, S. C.: See FOX, G. M., 163, 656
 PHILLIPS, D.: See MACRAE, S. M., 792
 PHILLIPS, P. C.: See BRUGGERS, C. S., 719
 PLOTNIK, R. D.: See MANNIS, M. J., 480
 PORTNOY, S. L., ARFFA, R. C., JOHNSON, B. L., and TERNER, I. S.: Metastatic renal cell carcinoma of the iris manifesting as an intrastromal iris cyst (letter), 113
 PRAGER, T. C.: See ARMESTO, D. M., 407
 PRAGER, T. C.: See GOOSEY, J. D., 145
 PRAGER, T. C.: See HOLLADAY, J. T., 372
 PROSPECTIVE EVALUATION OF RADIAL KERATOTOMY STUDY GROUP, THE: See WARING, G. O., III, 133
 PROTZKO, E. E.: See RAYMOND, W. R., IV, 633
 PRUETT, R. C.: See CELORIO, J. M., 20
 PRUETT, R. C.: See WU, G., 294
 PRUM, B. E., JR., SHIELDS, S. R., SHIELDS, M. B., HICKINGBOTHAM, D., and CHANDLER, D. B.: In vitro videographic comparison of argon and Nd:YAG laser iridotomy, 589

Q

- QUARANTA, L.: See TRIPATHI, R. C., 247

R

- RAMAKRISHNAN, M.: See FICKER, L., 473
 RAMOCKI, J. M.: See SPOOR, T. C., 724
 RAO, N. A.: See DUGEL, P. U., 118
 RAO, N. A.: See FORSTER, D. J., 256, 380
 RAYMOND, W. R., IV, CHAR, D. H., NORMAN, D., and PROTZKO, E. E.: Magnetic resonance imaging evaluation of uveal tumors, 633
 REALE, F.: See WEISS, J. S., 648
 REID, T. K.: See TESKE, M. P., 522
 REINECKE, R. D.: See GOTTLÖB, I., 71, 658
 REIVICH, M.: See BOSLEY, T. M., 413
 RESNICK, S. C.: See LEWIS, H., 197
 REYNA, G. S.: See CRUZ, O. A., 703
 REYNOLDS, R. D., NELSON, L. B., and GREENWALD, M. J.: Large refractive change after strabismus surgery (letter), 371
 ROBIN, A. L.: See DIEHL, D. L. C., 351
 RODRIGUEZ, F. J., LEWIS, H., KREIGER, A. E., YOSHIZUMI, M. O., and SIDIKARO, Y.: Scleral buckling for rhegmatogenous retinal detachment associated with severe myopia, 595
 ROGERS, G. L.: See LEGUIRE, L. E., 427
 ROGERS, G. L.: See SAUNDERS, R. A., 658
 ROHRBACH, J. M.: See STEUHL, K.-P., 312
 ROMÁN, A. J.: See JACOBSON, S. G., 446
 ROMÁN, M. I.: See JACOBSON, S. G., 446
 RONCIN, J.-P.: See NORDMANN, J.-P., 651
 RONDEAU, M. J.: See SILVERMAN, R. H., 327
 ROSEN, C. E.: See SLAMOVITS, T. L., 209
 ROSENBLATT, M.: See TEICH, S. A., 118
 ROSENBLUM, J. L.: See BERGER, A. S., 774
 ROSNER, B.: See BERSON, E. L., 614
 ROUSSEL, T. J.: See FOX, G. M., 163, 656
 ROWSEY, J. J.: See WARING, G. O., III, 133
 ROZENBAUM, D.: See KREMER, I., 375
 RUBINFELD, R. S., MACRAE, S. M., and LAIBSON, P. R.: Successful treatment of recurrent corneal erosion with Nd:YAG anterior stromal puncture (correspondence), 252
 RUIZ, R. S., and SAATCI, O. A.: Extracapsular cataract extraction with intraocular lens implantation after scleral buckling surgery, 174
 RUIZ, R. S., and SAATCI, O. A.: Posterior chamber intraocular lens implantation in eyes with inactive and active proliferative diabetic retinopathy, 158
 RYAN, S. J.: Michels, Ronald G. 1943-1991 (obituary), 661

S

- SAATCI, O. A.: See RUIZ, R. S., 158, 174
 SABATES, F. N., JR., TSAI, F., SABATES, N. R., and BLITSTEIN, B.: Transient cranial nerve palsies after cavernous sinus fistula embolization (letter), 771
 SABATES, N. R.: See SABATES, F. N., JR., 771
 SACKS, R. D., STOCK, E. L., CRAWFORD, S. E., GREENWALD, M. J., and O'GRADY, R. B.: Scleritis and Wegener's granulomatosis in children, 430
 SANDBERG, M. A.: See BERSON, E. L., 614
 SANDERSON, J. C.: See GOOSEY, J. D., 145
 SARAUX, H.: See NORDMANN, J.-P., 651
 SATTTLER, F.: See DUGEL, P. U., 118
 SAUNDERS, R. A., and ROGERS, G. L.: Surgical management of oculomotor nerve palsy (correspondence), 658
 SAVINO, P. J.: See BOSLEY, T. M., 413
 SCHANZLIN, D. J.: See KINCAID, M. C., 374
 SCHÖNHERR, U.: See LANG, G. E., 243
 SCHWAB, I. R.: The epidemiologic association of Fuchs' heterochromic iridocyclitis and ocular toxoplasmosis, 356
 SCHWAB, I. R.: See MANNIS, M. J., 480
 SCHWARTZ, A. E.: See MUSCH, D. C., 739
 SCHWARTZ, B.: See O'BRIEN, C., 491
 SCOTT, C.: See MACRAE, S. M., 792

- SEAL, D.: See FICKER, L., 473
- SEN, A. K.: See BHALLA, J. S., 114
- SERGOTT, R. C.: See BOSLEY, T. M., 413
- SETOGAWA, T.: See HAYASAKA, S., 379
- SHAKIN, E. P.: See DUKER, J. S., 255
- SHARMA, Y. R.: See VAJPAYEE, R. B., 715
- SHIELDS, C. L., SHIELDS, J. A., EAGLE, R. C., JR., and DE POTTER, P.: Histopathologic evidence of fibrovascular ingrowth four weeks after placement of the hydroxyapatite orbital implant, 363
- SHIELDS, J. A.: See SHIELDS, C. L., 363
- SHIELDS, M. B.: See MAO, L. K., 51
- SHIELDS, M. B.: See MILLER, K. N., 323
- SHIELDS, M. B.: See PRUM, B. E., JR., 589
- SHIELDS, M. B.: See WILKERSON, M., 105
- SHIELDS, S. R.: See PRUM, B. E., JR., 589
- SHIN, D. H.: See ZEITER, J. H., 581
- SIDIKARO, Y.: See RODRIGUEZ, F. J., 595
- SILVERMAN, R. H., VOGELSANG, B., RONDEAU, M. J., and COLEMAN, D. J.: Therapeutic ultrasound for the treatment of glaucoma, 327
- SIMON, J. W.: See CASTRONUOVO, S., 419
- SLAMOVITS, T. L., ROSEN, C. E., CHENG, K. P., and STRIPH, G. G.: Visual recovery in patients with optic neuritis and visual loss to no light perception, 209
- SLUSHER, M. M.: See GREVEN, C. M., 103
- SMITH, R. E.: See MACRAE, S. M., 792
- SMITH, R. E.: See WARING, G. O., III, 133
- SMITH, T. J.: See PEARSON, P. A., 773
- SMOLIN, G.: See UPADHYAY, M. P., 92
- SNYDER, J. W.: See BOWE, B. E., 686
- SOLOMON, K. D.: See PEARSON, P. A., 773
- SPAETH, G. L.: Anisocoria in the pigmentary dispersion syndrome (correspondence), 384
- SPECTOR, R. H.: Echographic diagnosis of dural carotid-cavernous sinus fistulas, 77
- SPIERER, A., DESATNIK, H., and BARISHAK, Y. R.: Aberrant extraocular fibrous band as a cause of strabismus (letter), 370
- SPOOR, T. C., HARTEL, W. C., LENSINK, D. B., and WILKINSON, M. J.: Treatment of traumatic optic neuropathy with corticosteroids—correction (correspondence), 526
- SPOOR, T. C., WILKINSON, M. J., and RAMOCKI, J. M.: Optic nerve sheath decompression for the treatment of progressive nonarteritic ischemic optic neuropathy, 724
- STEINSAPIR, K.: See TRIPATHI, R. C., 247
- STERN, G. A.: See DRIEBE, W. T., JR., 256
- STEUHL, K.-P., KNORR, M., ROHRBACH, J. M., LISCH, W., KAISERLING, E., and THIEL, H.-J.: Paraproteinemic corneal deposits in plasma cell myeloma, 312
- STEWART, W. C.: See MAO, L. K., 51
- STOCK, E. L.: See SACKS, R. D., 430
- STRAATSMA, B. R.: See LEWIS, H., 197
- STRAHLMAN, E. R.: See WARING, G. O., III, 133
- STRIPH, G. G.: See SLAMOVITS, T. L., 209
- STULTING, R. D.: See MACRAE, S. M., 792
- STULTING, R. D.: See MADER, T. H., 377
- SUGAR, A.: See MUSCH, D. C., 739
- SUGIN, S. L., HENDERLY, D. E., FRIEDMAN, S. M., JAMPOL, L. M., and DOYLE, J. W.: Unilateral frosted branch angiitis, 682
- SUMMERS, C. G.: See MEIUSI, R. S., 108
- SWARTZ, M.: See TESKE, M. P., 522
- T**
- TAKAI, S.: See KINOSHITA, S., 307
- TAKAMOTO, T.: See O'BRIEN, C., 491
- TAKANASHI, T.: See OGURA, Y., 179
- TANAKA, F.: See KINOSHITA, S., 307
- TANNENBAUM, M. H.: See ZAGELBAUM, B. M., 248
- TAYLOR, H. R.: See ADAMSONS, I., 65
- TAYLOR, K. I.: See ADAMSONS, I., 65
- TEICH, S. A., ROSENBLATT, M., and FRIEDMAN, A. H.: *Pneumocystis carinii* choroiditis after long-term aerosolized pentamidine therapy (correspondence), 118
- TERNER, I. S.: See PORTNOY, S. L., 113
- TESKE, M. P., REID, T. K., TWEETEN, J. P., and SWARTZ, M.: Ichthyosis and crystalline maculopathy (letter), 522
- THIEL, H.-J.: See STEUHL, K.-P., 312
- THOMAS, M. A., and KAPLAN, H. J.: Surgical removal of subfoveal neovascularization in the presumed ocular histoplasmosis syndrome, 1
- THOMPSON, H. S.: Laser Surgery of the Posterior Segment, by Bloom, S. M., and Brucker, A. J. (book review), 388
- THOMPSON, H. S.: See BURDE, R. M., 100
- THOMPSON, P.: Visual Allusions. Pictures of Perception, by Wade, N. (book review), 386
- TIEDEMAN, J. S.: A physical analysis of the factors that determine the contour of the iris, 338
- TITIYAL, J. S.: See VAJPAYEE, R. B., 715
- TOWNSHEND, L. M.: See BUCKLEY, E. G., 302
- TREISTER, G.: See BARTOV, E., 501
- TRIPATHI, B. J.: See TRIPATHI, R. C., 247
- TRIPATHI, R. C., TRIPATHI, B. J., PARK, J. K., QUARANTA, L., STEINSAPIR, K., LEHMAN, E., and ERNEST, J. T.: Intracameral tissue plasminogen activator for resolution of fibrin clots after glaucoma filtering procedures (letter), 247
- TSAI, F.: See SABATES, F. N., JR., 771
- TSAI, J. C.: See ASSIA, E. I., 628

- TSO, P. C.: See DREHER, A. W., 221
 TSUBOTA, K.: The importance of the Schirmer test with nasal stimulation (letter), 106
 TUFT, S. J.: See DAVISON, C. R., 690
 TULADHAR, N. R.: See UPADHYAY, M. P., 92
 TUULONEN, A., and AIRAKSINEN, P. J.: Initial glaucomatous optic disk and retinal nerve fiber layer abnormalities and their progression, 485
 TWEETEN, J. P.: See TESKE, M. P., 522
 TYCHSEN, L.: See BERGER, A. S., 774

U

- UPADHYAY, M. P., KARMACHARYA, P. C. D., KOIRALA, S., TULADHAR, N. R., BRYAN, L. E., SMOLIN, G., and WHITCHER, J. P.: Epidemiologic characteristics, predisposing factors, and etiologic diagnosis of corneal ulceration in Nepal, 92

V

- VAJPAYEE, R. B., ANGRA, S. K., TITIYAL, J. S., SHARMA, Y. R., and CHABBRA, V. K.: Pseudophakic pupillary-block glaucoma in children, 715
 VAN DEN BERG, W.: See VERBRAAK, F. D., 111
 VAN LANGENHOVE, L.: See DE KEYSER, J., 516
 VAN NOUHUYS, C. E.: Signs, complications, and platelet aggregation in familial exudative vitreoretinopathy, 34
 VASHISHT, S.: See BHALLA, J. S., 114
 VERBRAAK, F. D., VAN DEN BERG, W., and BOS, P. J. M.: Retinal pigment epitheliopathy in acute leukemia (letter), 111
 VOGELSANG, B.: See SILVERMAN, R. H., 327
 VON NOORDEN, G. K.: In defense of animal research (editorial), 367
 VON WEYMARN, C.: See DE POTTER, P., 276

W

- WALL, M.: Clinical Tests of Vision, by Frisén, L. (book review), 386
 WALLACE, D. C.: See NEWMAN, N. J., 750
 WAND, M.: See DIEHL, D. L. C., 351
 WANGER, P.: See MARTIN-BOGLIND, L. M., 711
 WARING, G. O., III, LYNN, M. J., STRAHLMAN, E. R., KUTNER, M. H., CULBERTSON, W., LAIBSON, P. R., LINDSTROM, R. D., McDONALD, M. B., MYERS, W. D., OBSTBAUM, S. A., ROWSEY, J. J., SMITH, R. E., and PROSPECTIVE EVALUATION OF RADIAL KERATOTOMY STUDY GROUP, THE: Stability of refraction during four years after radial keratotomy in the Prospective Evaluation of Radial Keratotomy Study, 133
 WATTS, L. E.: See GREVEN, C. M., 103
 WEAVER, R. G.: See GREVEN, C. M., 103
 WEIGEL-DIFRANCO, C.: See BERSON, E. L., 614

- WEINREB, R. N.: See DREHER, A. W., 221
 WEINSTEIN, J.: Thyroid Eye Disease, ed. 2, by Char, D. H. (book review), 122
 WEISS, H.: See HAIMANN, M. H., 656
 WEISS, J. S., PERUSSE, P., and REALE, F.: Tear cytology in conjunctival melanoma (letter), 648
 WELEBER, R. G.: See WILSON, D. J., 24
 WHIPPLE, D.: See MACRAE, S. M., 792
 WHITACRE, M. M., EMIG, M., and HASSANEIN, K.: The effect of Perkins, Tono-Pen, and Schiötz tonometry on intraocular pressure, 59
 WHITCHER, J. P.: See UPADHYAY, M. P., 92
 WHITE, W. L., and HOLLSTEN, D. A.: A new instrument for use in evisceration (letter), 115
 WIEK, J.: See HANSEN, L. L., 525
 WIENER, M. D.: See BRUGGERS, C. S., 719
 WILES, S. B., and IDE, C. H.: *Clostridium perfringens* endophthalmitis (letter), 654
 WILES, S. B., MACKENZIE, D., and IDE, C. H.: Control of intraocular pressure with apraclonidine hydrochloride after cataract extraction, 184
 WILHELMUS, K. R., HAMILL, M. B., and JONES, D. B.: Varicella disciform stromal keratitis, 575
 WILKERSON, M., LEWIS, R. A., and SHIELDS, M. B.: Follicular conjunctivitis associated with apraclonidine (letter), 105
 WILKINSON, C. P.: See MACRAE, S. M., 792
 WILKINSON, M. J.: See SPOOR, T. C., 526, 724
 WILSON, D. J., WELEBER, R. G., and GREEN, W. R.: Ocular clinicopathologic study of gyrate atrophy, 24
 WILSON, S. E.: Lacrimal gland epidermal growth factor production and the ocular surface, 763
 WINTER, F. C.: Eye Diseases in Hot Climates, ed. 2, by Sandford-Smith, J. (book review), 259
 WITKOP, C. J.: See CASTRONUOVO, S., 419
 WIZNIA, R. A., and PEARSON, W. N.: Use of transesophageal echocardiography for detection of a likely source of embolization to the central retinal artery (letter), 104
 WOLF, B.: See CASTRONUOVO, S., 419
 WRIGHT, M. M.: See ANDERSON, D. R., 344
 WRIGHT, P.: See FICKER, L., 473
 WU, D. C.: See O'BRIEN, C., 491
 WU, G., PRUETT, R. C., BALDINGER, J., and HIROSE, T.: Hereditary hemorrhagic macular dystrophy, 294
 WU, Y. H.: See LIN, C. P., 251

Y

YOSHIZUMI, M. O.: See RODRIGUEZ, F. J., 595

YUE, B. Y. J. T.: See ELNER, S. G., 84

Z

ZAGELBAUM, B. M., TANNENBAUM, M. H., and
HERSH, P. S.: *Candida albicans* corneal ulcer as-
sociated with crack cocaine (letter), 248

ZEITER, J. H., SHIN, D. H., and BAEK, N. H.: Visual
field defects in diabetic patients with primary
open-angle glaucoma, 581

ZILIS, J. D., and MACHEMER, R.: Light damage in
detached retina, 47

ZIMMERMAN, R.: See BOSLEY, T. M., 413

ZOGRAFOS, L.: See DE POTTER, P., 276

ABSTRACT INDEX

A

***Acanthamoeba* sp.**

In vivo and in vitro collagenolytic activity of *Acanthamoeba castellanii*, 530

Acetazolamide

Acetazolamide-associated aplastic anemia, 789

Long-term effect of acetazolamide in a patient with retinitis pigmentosa, 267

Acquired immunodeficiency syndrome

A controlled trial of early adjunctive treatment with corticosteroids for *Pneumocystis carinii* pneumonia in the acquired immunodeficiency syndrome, 531

Extracorporeal photopheresis in the treatment of AIDS-related complex. A pilot study, 396

Alcoholism

Population and pedigree studies reveal a lack of association between the dopamine D₂ receptor gene and alcoholism, 667

Aldose reductase

A randomized trial of sorbinil, an aldose reductase inhibitor, in diabetic retinopathy, 261

Allergy

Reduced allergen-induced nasal congestion and leukotriene synthesis with an orally active 5-lipoxygenase inhibitor, 668

Amblyopia

A longitudinal study of a population based sample of astigmatic children. 1. Refraction and amblyopia, 129

Visual impairment in a rural Appalachian community. Prevalence and causes, 400

Amniocentesis

Ophthalmic complications of amniocentesis, 790

Anemia

Acetazolamide-associated aplastic anemia, 789

Aniridia

A mouse model of the aniridia-Wilms tumor deletion syndrome, 397

Antibody

Antibodies to Epstein-Barr virus in iridocorneal endothelial syndrome, 530

Antigen

Spontaneous inflammatory disease in transgenic rats expressing HLA-B27 and human β_2m . An animal model of HLA-B27-associated human disorders, 787

***Aspergillus* sp.**

Synthetic analogues of fumagillin that inhibit angiogenesis and suppress tumor growth, 534

Aspirin

European stroke prevention study, 396

Astigmatism

A longitudinal study of a population based sample of astigmatic children. 1. Refraction and amblyopia, 129

Atherosclerosis

Regression of coronary artery disease as a result of intensive lipid-lowering therapy in men with high levels of apolipoprotein B, 401

B

Beta-blocker

Topical timolol decreases plasma high-density lipoprotein cholesterol level, 262

Blepharospasm

Saccadic eye movements in essential blepharospasm, 126

C

Caffeine

Coffee, caffeine, and cardiovascular disease in men, 263

Cancer

Cell proliferation in carcinogenesis, 264

Overall mortality and cancer mortality around French nuclear sites, 401

Relation of meat, fat, and fiber intake to the risk of colon cancer in a prospective study among women, 531

***Candida* sp.**

A randomized, double-blind trial of nystatin therapy for the candidiasis hypersensitivity syndrome, 667

Capsulotomy

Displacement of bag-placed hydrogel lenses into the vitreous following neodymium:YAG laser capsulotomy, 124

Cardiovascular effects

Coffee, caffeine, and cardiovascular disease in men, 263

Carotid artery

Carotid endarterectomy for chronic retinal ischemia, 784

Cataract

Delayed eye and other consequences from exposure to methyl isocyanate. 93% follow up of exposed and unexposed cohorts in Bhopal, 130

Effect of a resutured iridotomy on glare disability in glaucoma patients having cataract surgery, 788

Epidemiologic evidence of a role for the antioxidant vitamins and carotenoids in cataract prevention, 664

A possible role for vitamins C and E in cataract prevention, 664

Randomized single blind trial to compare the toxicity of subconjunctival gentamicin and cefuroxime in cataract surgery, 664

Visual impairment in a rural Appalachian community. Prevalence and causes, 400

Cefuroxime

Randomized single blind trial to compare the toxicity of subconjunctival gentamicin and cefuroxime in cataract surgery, 664

Central nervous system

Central nervous system involvement in Von Hippel-Lindau disease, 783

Cerebrovascular disease

Cerebrovascular complications of the use of the "crack" form of alkaloidal cocaine, 263

Children

A longitudinal study of children with a family history of strabismus. Factors determining the incidence of strabismus, 397

A randomized, prospective field trial of a conjugate vaccine in the protection of infants and young children against invasive *Haemophilus influenzae* type b disease, 533

Use of high dose chloral hydrate for ophthalmic exams in children. A retrospective review of 302 cases, 533

Chloral hydrate

Use of high dose chloral hydrate for ophthalmic exams in children. A retrospective review of 302 cases, 533

Cholesterol

The human lens after 48 weeks of treatment with lovastatin, 125

Topical timolol decreases plasma high-density lipoprotein cholesterol level, 262

Choroideremia

Cloning of a gene that is rearranged in patients with choroideraemia, 124

Cocaine

Cerebrovascular complications of the use of the "crack" form of alkaloidal cocaine, 263

Collagen

Epikeratoplasty technique without suture using human collagen type IV lenticules. Experimental study on monkey, 262

In vivo and in vitro collagenolytic activity of *Acanthamoeba castellanii*, 530

Congenital disorders

Maternal outcome after open fetal surgery. A review of the first 17 human cases, 787

What is known about the prevention of congenital toxoplasmosis?, 396

Conjunctiva

Staining of the conjunctiva and conjunctival tear film, 129

Contact lens

Contact lens surface deposits increase the adhesion of *Pseudomonas aeruginosa*, 262

Contrast sensitivity

Peripheral contrast sensitivity in glaucoma and ocular hypertension, 666

Cornea

Epikeratoplasty technique without suture using human collagen type IV lenticules. Experimental study on monkey, 262

Laser-induced occlusion of corneal blood vessels with variable emission and absorption, 399

Coronary artery

Regression of coronary artery disease as a result of intensive lipid-lowering therapy in men with high levels of apolipoprotein B, 401

Corticosteroid

A controlled trial of early adjunctive treatment with corticosteroids for *Pneumocystis carinii* pneumonia in the acquired immunodeficiency syndrome, 531

Cryotherapy

Multicenter trial of cryotherapy for retinopathy of prematurity. One-year outcome. Structure and function, 402

D

Diabetes

Biometry of the crystalline lens in early-onset diabetes, 398

Induction of donor-specific unresponsiveness by intrathymic islet transplantation, 264

Plasma prorenin activity and complications in children with insulin-dependent diabetes mellitus, 261

A prospective study of the development of diabetes in relatives of patients with insulin-dependent diabetes, 126

Slow glucose removal rate and hyperinsulinemia precede the development of type II diabetes in the offspring of diabetic parents, 528

Diabetic retinopathy

Central visual field changes after panretinal photocoagulation in proliferative diabetic retinopathy, 261

Comparison of non-mydratic retinal photography with ophthalmoscopy in 2159 patients. Mobile retinal camera study, 669

Fifteen-year argon laser and xenon photocoagulation results of Bascom Palmer Eye Institute's patients participating in the Diabetic Retinopathy Study, 789

A randomized trial of sorbinil, an aldose reductase inhibitor, in diabetic retinopathy, 261

Ticlopidine treatment reduces the progression of nonproliferative diabetic retinopathy, 528

Diclofenac

Diclofenac-associated hepatotoxicity, 532

Dioxin

Health status of Air Force veterans occupationally exposed to herbicides in Vietnam. I. Physical health, 265

Health status of Air Force veterans occupationally exposed to herbicides in Vietnam. II. Mortality, 265

Dipyridamole

European stroke prevention study, 396

Dopamine

Population and pedigree studies reveal a lack of association between the dopamine D₂ receptor gene and alcoholism, 667

Drusen

Relationship of drusen and abnormalities of the retinal pigment epithelium to the prognosis of neovascular macular degeneration, 403

E

Edema

Zidovudine-induced macular edema, 789

Environmental illness

Environmental illness. A controlled study of 28 subjects with "20th century disease", 667

Enzyme

In vivo and in vitro collagenolytic activity of *Acanthamoeba castellanii*, 530

Epikeratophakia

Epikeratoplasty technique without suture using human collagen type IV lenticules. Experimental study on monkey, 262

Epikeratoplasty

Epikeratoplasty technique without suture using human collagen type IV lenticules. Experimental study on monkey, 262

Epstein-Barr virus

Antibodies to Epstein-Barr virus in iridocorneal endothelial syndrome, 530

Three cases of EB virus-associated uveitis, 402

Esotropia

A longitudinal study of children with a family history of strabismus. Factors determining the incidence of strabismus, 397

Extraocular muscle

Significance of cytotoxic eye muscle antibodies in patients with thyroid-associated ophthalmopathy, 669

Why are eye muscles frequently involved in myasthenia gravis?, 529

Eyelid

Delayed eye and other consequences from exposure to methyl isocyanate. 93% follow up of exposed and unexposed cohorts in Bhopal, 130

F

Fibroblast growth factor

Photoreceptor degeneration in inherited retinal dystrophy delayed by basic fibroblast growth factor, 266

Filtering surgery

Subconjunctival THC:YAG laser limbal sclerostomy ab externo in the rabbit, 125

Fluorescein angiography

Ticlopidine treatment reduces the progression of nonproliferative diabetic retinopathy, 528

Fuchs' dystrophy

The association of Fuchs's corneal endothelial dystrophy with axial hypermetropia, shallow anterior chamber, and angle closure glaucoma, 398

G

Genetics

Cloning of a gene that is rearranged in patients with choroideraemia, 124

A mouse model of the aniridia-Wilms tumor deletion syndrome, 397

Mutations within the rhodopsin gene in patients with autosomal dominant retinitis pigmentosa, 397

Retinal degeneration in the rd mouse is caused by a defect in the β subunit of rod cGMP-phosphodiesterase, 124

Spontaneous inflammatory disease in transgenic rats expressing HLA-B27 and human β_2m . An animal model of HLA-B27-associated human disorders, 787

Gentamicin

Randomized single blind trial to compare the toxicity of subconjunctival gentamicin and cefuroxime in cataract surgery, 664

Glare

Effect of a resutured iridotomy on glare disability in glaucoma patients having cataract surgery, 788

Glaucoma

The association of Fuchs's corneal endothelial dystrophy with axial hypermetropia, shallow anterior chamber, and angle closure glaucoma, 398

Effect of a resutured iridotomy on glare disability in glaucoma patients having cataract surgery, 788

The glaucoma laser trial (GLT). 2. Results of argon laser trabeculoplasty versus topical medicines, 399

The impact of intraocular pressure on visual field loss in primary open angle glaucoma, 666

Long-term efficacy of primary laser trabeculoplasty, 788

Peripheral contrast sensitivity in glaucoma and ocular hypertension, 666

Glomerulonephritis

Subretinal neovascular membranes associated with chronic membranoproliferative glomerulonephritis type II, 670

Glucose

Cerebral glucose metabolism in adults with hyperactivity of childhood onset, 528

Slow glucose removal rate and hyperinsulinemia precede the development of type II diabetes in the offspring of diabetic parents, 528

Glycine

Visual disturbances, serum glycine levels and transurethral resection of the prostate, 267

Guanosine monophosphate

Nitric oxide. A novel signal transduction mechanism for transcellular communication, 535

H***Haemophilus* sp.**

A randomized, prospective field trial of a conjugate vaccine in the protection of infants and young children against invasive *Haemophilus influenzae* type b disease, 533

Health care costs

Comparison of uninsured and privately insured hospital patients. Condition on admission, resource use, and outcome, 786

The direct costs of universal precautions in a teaching hospital, 128

Illness severity and costs of admissions at teaching and nonteaching hospitals, 127

Predicting the appropriate use of carotid endarterectomy, upper gastrointestinal endoscopy, and coronary angiography, 127

Health care delivery

Hispanic health in the United States. Council on Scientific Affairs, 786

Incidence of adverse events and negligence in hospitalized patients. Results of the Harvard Medical Practice Study I, 785

The nature of adverse events in hospitalized patients. Results of the Harvard Medical Practice Study II, 785

A public hospital closes. Impact on patients' access to care and health status, 532

Health insurance

The association of payer with utilization of cardiac procedures in Massachusetts, 128

Comparison of uninsured and privately insured hospital patients. Condition on admission, resource use, and outcome, 786

Hemianopsia

Extrageniculate vision in hemianopic humans. Saccade inhibition by signals in the blind field, 268

Hepatitis

Diclofenac-associated hepatotoxicity, 532

Herbicide

Health status of Air Force veterans occupationally exposed to herbicides in Vietnam. I. Physical health, 265

Health status of Air Force veterans occupationally exposed to herbicides in Vietnam. II. Mortality, 265

Hernia

The opposite pupil in herniation, 529

Human immunodeficiency virus

Detection of a human intracisternal A-type retroviral particle antigenically related to HIV, 670

Infection with human immunodeficiency virus type 1 (HIV-1) among recipients of antibody-positive blood donations, 400

Risk for occupational transmission of human immunodeficiency virus type 1 (HIV-1) associated with clinical exposures. A prospective evaluation, 400

Zidovudine-induced macular edema, 789

Hyperactivity

Cerebral glucose metabolism in adults with hyperactivity of childhood onset, 528

Hyperinsulinemia

Slow glucose removal rate and hyperinsulinemia precede the development of type II diabetes in the offspring of diabetic parents, 528

Hypermetropia

The association of Fuchs's corneal endothelial dystrophy with axial hypermetropia, shallow anterior chamber, and angle closure glaucoma, 398

A longitudinal study of children with a family history of strabismus. Factors determining the incidence of strabismus, 397

Hypertension

Peripheral contrast sensitivity in glaucoma and ocular hypertension, 666

I**Infants**

Multicenter trial of cryotherapy for retinopathy of prematurity. One-year outcome. Structure and function, 402

Ophthalmic complications of amniocentesis, 790

Injuries

Sports-related ocular trauma, 398

Internal medicine

How satisfying is the practice of internal medicine? A national survey, 784

Intraocular lens

Displacement of bag-placed hydrogel lenses into the vitreous following neodymium:YAG laser capsulotomy, 124

Visual results and complications of transsclerally sutured intraocular lenses in penetrating keratoplasty, 124

Intraocular pressure

The impact of intraocular pressure on visual field loss in primary open angle glaucoma, 666

Iridotomy

Effect of a resutured iridotomy on glare disability in glaucoma patients having cataract surgery, 788

Ischemia

Carotid endarterectomy for chronic retinal ischemia, 784

European stroke prevention study, 396

Regional myocardial metabolism of high-energy phosphates during isometric exercise in patients with coronary artery disease, 535

Scatter photocoagulation restores tissue hypoxia in experimental vasoproliferative microangiopathy in miniature pigs, 403

Ivermectin

Impact of mass treatment of onchocerciasis with ivermectin on the transmission of infection, 267

L**Lacrimal apparatus**

Staining of the conjunctiva and conjunctival tear film, 129

Laser

Displacement of bag-placed hydrogel lenses into the vitreous following neodymium:YAG laser capsulotomy, 124

Fifteen-year argon laser and xenon photocoagulation results of Bascom Palmer Eye Institute's patients participating in the Diabetic Retinopathy Study, 789

The glaucoma laser trial (GLT). 2. Results of argon laser trabeculoplasty versus topical medicines, 399

Laser-induced occlusion of corneal blood vessels with variable emission and absorption, 399

Long-term efficacy of primary laser trabeculoplasty, 788

Quantitative analysis of retinal hemodynamics using targeted dye delivery, 533

Scatter photocoagulation restores tissue hypoxia in experimental vasoproliferative microangiopathy in miniature pigs, 403

Subconjunctival THC:YAG laser limbal sclerostomy ab externo in the rabbit, 125

Lens

Biometry of the crystalline lens in early-onset diabetes, 398

The human lens after 48 weeks of treatment with lovastatin, 125

Precapsular film on the aging human lens. Precursor of pseudoexfoliation?, 664

Leukemia

Overall mortality and cancer mortality around French nuclear sites, 401

Lovastatin

The human lens after 48 weeks of treatment with lovastatin, 125

M**Macula**

Hematogenous photosensitization. A mechanism for the development of age-related macular degeneration, 266

Relationship of drusen and abnormalities of the retinal pigment epithelium to the prognosis of neovascular macular degeneration, 403

Risk of developing a macular hole, 129

Zidovudine-induced macular edema, 789

Macular degeneration

Hematogenous photosensitization. A mechanism for the development of age-related macular degeneration, 266

Relationship of drusen and abnormalities of the retinal pigment epithelium to the prognosis of neovascular macular degeneration, 403

Second eye involvement in age-related macular degeneration. A four-year prospective study, 783

Visual impairment in a rural Appalachian community. Prevalence and causes, 400

Magnetic resonance imaging

Clinical and magnetic resonance imaging in optic neuritis, 783

Regional myocardial metabolism of high-energy phosphates during isometric exercise in patients with coronary artery disease, 535

Medical economics

Attitudes of internal medicine faculty and residents toward professional interaction with pharmaceutical sales representatives, 128

Medical education

The status of women at one academic medical center. Breaking through the glass ceiling, 265

Medical journals

Loose connections between peer-reviewed clinical journals and clinical practice, 401

Medical legislation

The orphan drug act. The first 7 years, 786

Medical malpractice

Medical malpractice—the Canadian experience, 784

Medicare

Predicting the appropriate use of carotid endarterectomy, upper gastrointestinal endoscopy, and coronary angiography, 127

Methyl isocyanate

Delayed eye and other consequences from exposure to methyl isocyanate. 93% follow up of exposed and unexposed cohorts in Bhopal, 130

Microcephaly

Vision despite tomographic absence of the occipital cortex, 529

Multiple sclerosis

Clinical and magnetic resonance imaging in optic neuritis, 783

Myasthenia gravis

Why are eye muscles frequently involved in myasthenia gravis?, 529

Mydriasis

Time course of thymoxamine reversal of phenylephrine-induced mydriasis, 668

N**Neoplasia**

Paraneoplastic pemphigus. An autoimmune mucocutaneous disease associated with neoplasia, 668

Neovascularization

Laser-induced occlusion of corneal blood vessels with variable emission and absorption, 399

Relationship of drusen and abnormalities of the retinal pigment epithelium to the prognosis of neovascular macular degeneration, 403

Subretinal neovascular membranes associated with chronic membranoproliferative glomerulonephritis type II, 670

Synthetic analogues of fumagillin that inhibit angiogenesis and suppress tumor growth, 534

Nicotine

Ending smoking at The Johns Hopkins Medical Institutions. An evaluation of smoking prevalence and indoor air pollution, 127

Nitric oxide

Nitric oxide. A novel signal transduction mechanism for transcellular communication, 535

Nystagmus

Head shaking by visually impaired children. A voluntary neurovisual adaptation which can be confused with spasmodic nutans, 787

Nystatin

A randomized, double-blind trial of nystatin therapy for the candidiasis hypersensitivity syndrome, 667

O**Onchocerciasis**

Impact of mass treatment of onchocerciasis with ivermectin on the transmission of infection, 267

Open-angle glaucoma

The glaucoma laser trial (GLT). 2. Results of argon laser trabeculoplasty versus topical medicines, 399

The impact of intraocular pressure on visual field loss in primary open angle glaucoma, 666

Peripheral contrast sensitivity in glaucoma and ocular hypertension, 666

Ophthalmopathy

Significance of cytotoxic eye muscle antibodies in patients with thyroid-associated ophthalmopathy, 669

Optic neuritis

Clinical and magnetic resonance imaging in optic neuritis, 783

Orbit

Force necessary to fracture the orbital floor, 665

P**Paget's disease**

Prevalence of angioid streaks and other ocular complications of Paget's disease of bone, 398

Pancreas

Induction of donor-specific unresponsiveness by intrathymic islet transplantation, 264

Parkinson's disease

Reversal of experimental parkinsonism by lesions of the subthalamic nucleus, 126

Pemphigus

Paraneoplastic pemphigus. An autoimmune mucocutaneous disease associated with neoplasia, 668

Penetrating keratoplasty

Visual results and complications of transsclerally sutured intraocular lenses in penetrating keratoplasty, 124

Phenylephrine

Time course of thymoxamine reversal of phenylephrine-induced mydriasis, 668

Photocoagulation

Central visual field changes after panretinal photocoagulation in proliferative diabetic retinopathy, 261

Fifteen-year argon laser and xenon photocoagulation results of Bascom Palmer Eye Institute's patients participating in the Diabetic Retinopathy Study, 789

Scatter photocoagulation restores tissue hypoxia in experimental vasoproliferative microangiopathy in miniature pigs, 403

Photopheresis

Extracorporeal photopheresis in the treatment of AIDS-related complex. A pilot study, 396

Photoreceptor

Photoreceptor degeneration in inherited retinal dystrophy delayed by basic fibroblast growth factor, 266

***Pneumocystis* sp.**

A controlled trial of early adjunctive treatment with corticosteroids for *Pneumocystis carinii* pneumonia in the acquired immunodeficiency syndrome, 531

Pregnancy

Maternal outcome after open fetal surgery. A review of the first 17 human cases, 787

What is known about the prevention of congenital toxoplasmosis?, 396

Prostate

Visual disturbances, serum glycine levels and transurethral resection of the prostate, 267

Pseudoexfoliation syndrome

Precapsular film on the aging human lens. Precursor of pseudoexfoliation?, 664

***Pseudomonas* sp.**

Contact lens surface deposits increase the adhesion of *Pseudomonas aeruginosa*, 262

Pupil

The opposite pupil in herniation, 529

R**Retina**

Carotid endarterectomy for chronic retinal ischemia, 784

Central nervous system involvement in Von Hippel-Lindau disease, 783

Photoreceptor degeneration in inherited retinal dystrophy delayed by basic fibroblast growth factor, 266

Quantitative analysis of retinal hemodynamics using targeted dye delivery, 533

Retinal degeneration in the rd mouse is caused by a defect in the β subunit of rod cGMP-phosphodiesterase, 124

Scatter photocoagulation restores tissue hypoxia in experimental vasoproliferative microangiopathy in miniature pigs, 403

Subretinal neovascular membranes associated with chronic membranoproliferative glomerulonephritis type II, 670

Retinal pigment epithelium

Relationship of drusen and abnormalities of the retinal pigment epithelium to the prognosis of neovascular macular degeneration, 403

Retinitis pigmentosa

Long-term effect of acetazolamide in a patient with retinitis pigmentosa, 267

Mutations within the rhodopsin gene in patients with autosomal dominant retinitis pigmentosa, 397

Retinal degeneration in the rd mouse is caused by a defect in the β subunit of rod cGMP-phosphodiesterase, 124

Retinopathy

Central venous stasis retinopathy following the use of tranexamic acid, 534

Retinopathy of prematurity

Multicenter trial of cryotherapy for retinopathy of prematurity. One-year outcome. Structure and function, 402

Rhodopsin

Mutations within the rhodopsin gene in patients with autosomal dominant retinitis pigmentosa, 397

S**Saccades**

Extrageniculate vision in hemianopic humans. Saccade inhibition by signals in the blind field, 268

Saccadic eye movements in essential blepharospasm, 126

Sclerostomy

Subconjunctival THC:YAG laser limbal sclerostomy ab externo in the rabbit, 125

Sjögren's syndrome

Detection of a human intracisternal A-type retroviral particle antigenically related to HIV, 670

Smoking

Ending smoking at The Johns Hopkins Medical Institutions. An evaluation of smoking prevalence and indoor air pollution, 127

Sorbinil

A randomized trial of sorbinil, an aldose reductase inhibitor, in diabetic retinopathy, 261

Squamous cell carcinoma

Prevention of second primary tumors with isotretinoin in squamous-cell carcinoma of the head and neck, 264

Strabismus

A longitudinal study of a population based sample of astigmatic children. 1. Refraction and amblyopia, 129

A longitudinal study of children with a family history of strabismus. Factors determining the incidence of strabismus, 397

Stroke

European stroke prevention study, 396

T**Thymoxamine**

Time course of thymoxamine reversal of phenylephrine-induced mydriasis, 668

Ticlopidine

Ticlopidine treatment reduces the progression of nonproliferative diabetic retinopathy, 528

Timolol

Topical timolol decreases plasma high-density lipoprotein cholesterol level, 262

Tonometry

Tonometer utilization, accuracy, and calibration under field conditions, 666

Toxoplasmosis

What is known about the prevention of congenital toxoplasmosis?, 396

Trabeculoplasty

The glaucoma laser trial (GLT). 2. Results of argon laser trabeculoplasty versus topical medicines, 399

Long-term efficacy of primary laser trabeculoplasty, 788

Tumor

Central nervous system involvement in Von Hippel-Lindau disease, 783

Color Doppler imaging in the management of intraocular tumors, 665

A mouse model of the aniridia-Wilms tumor deletion syndrome, 397

Prevention of second primary tumors with isotretinoin in squamous-cell carcinoma of the head and neck, 264

Synthetic analogues of fumagillin that inhibit angiogenesis and suppress tumor growth, 534

U

Ultrasound

Color Doppler imaging in the management of intraocular tumors, 665

Uveitis

Three cases of EB virus-associated uveitis, 402

V

Vaccine

A randomized, prospective field trial of a conjugate vaccine in the protection of infants and young children against invasive *Haemophilus influenzae* type b disease, 533

Vein occlusion

Scatter photocoagulation restores tissue hypoxia in experimental vasoproliferative microangiopathy in miniature pigs, 403

Visual acuity

Head shaking by visually impaired children. A voluntary neurovisual adaptation which can be confused with spasmus nutans, 737

Visual disturbances, serum glycine levels and transurethral resection of the prostate, 267

Visual field

Central visual field changes after panretinal photocoagulation in proliferative diabetic retinopathy, 261

Extrageniculate vision in hemianopic humans. Saccade inhibition by signals in the blind field, 268

The impact of intraocular pressure on visual field loss in primary open angle glaucoma, 666

Vitamin

Epidemiologic evidence of a role for the antioxidant vitamins and carotenoids in cataract prevention, 664

A possible role for vitamins C and E in cataract prevention, 664

Vitreous

Risk of developing a macular hole, 129

Von Hippel-Lindau disease

Central nervous system involvement in Von Hippel-Lindau disease, 783

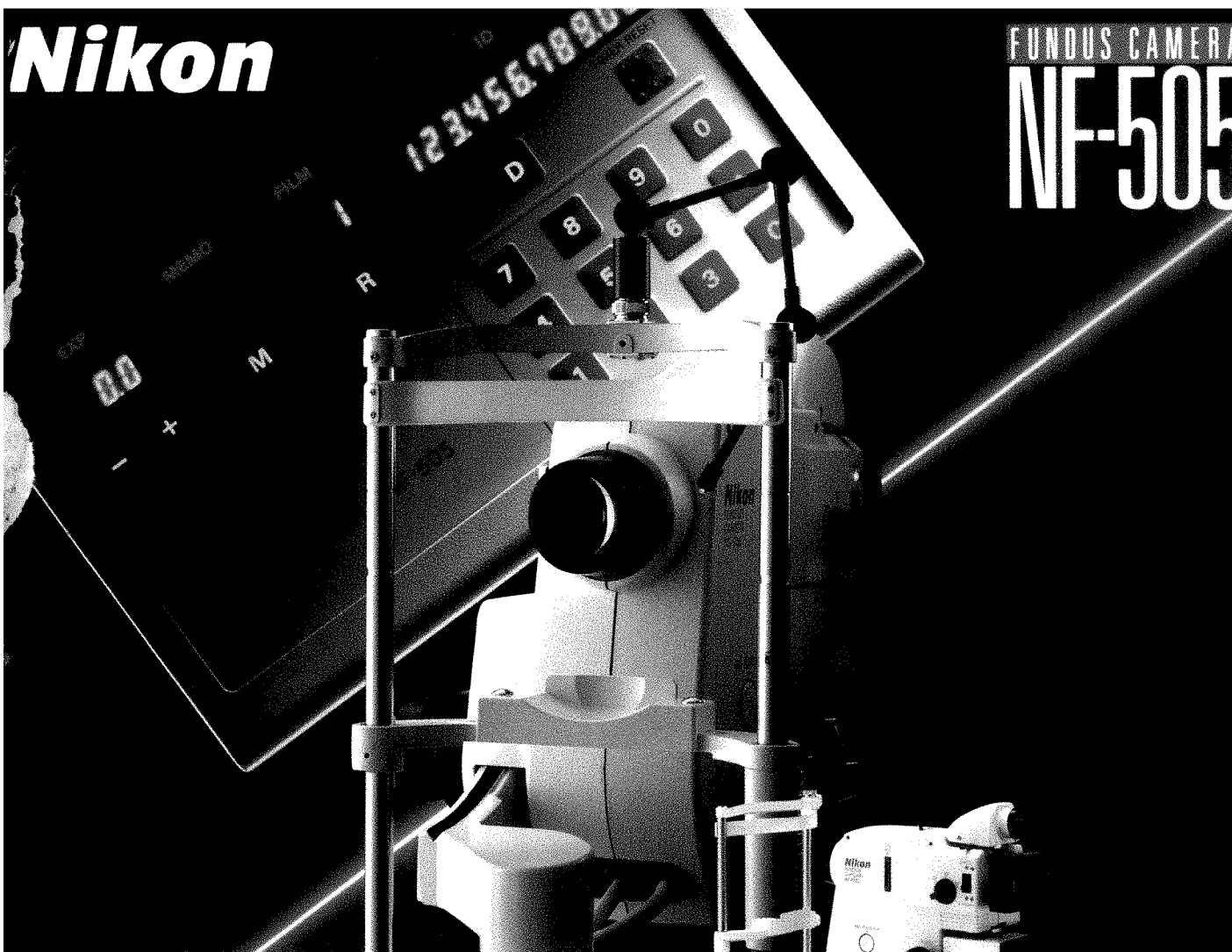
Z

Zidovudine

Zidovudine-induced macular edema, 789

Nikon

FUNDUS CAMERA
NF-505



Superb photo quality — the best reason for choosing Nikon's new Fundus Camera.

Nikon, the world's most respected optical maker, is proud to present the all new Fundus Camera NF-505. To meet the daily needs of eyecare professionals the world over, a whole list of truly useful features have been incorporated into the NF-505.

These include:

- Extremely precise image quality
- Shortened distance to the patient, yet a long 50.1mm distance to the cornea, for easy access to the patient
- Fluorescein photograph and widely applicable multi-band filters
- Program-auto exposure control
- Small-pupil device for working with 3.9mm pupil diameter
- Full 11-digit ID data imprint
- Brightly illuminated LED indications for operations in the dark
- Simplified objective lens cleaning
- The ability to accommodate wheelchair bound patients
- Variable viewing angle (50°, 30°, 20°)
- Full-circle instant photography

Easy to use, more powerful, and most important, uncompromising Nikon photo quality—three great reasons for choosing the all-new Nikon NF-505 fundus camera.

NIKON CORPORATION

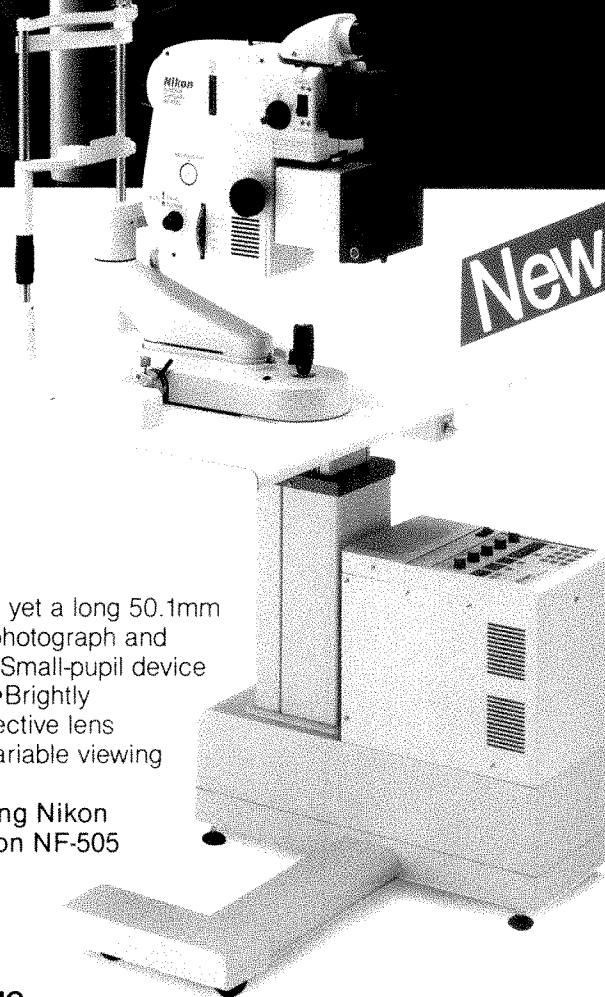
Fuji Bldg., 2-3, Marunouchi 3-chome, Chiyoda-ku, Tokyo 100, Japan
Tel: 81-3-3216-1031 Telex: 22601 (NIKON J) Fax: 81-3-3201-5856

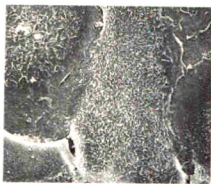
NIKON EUROPE B.V.

Schipholweg 321, P.O. Box 222, 1170 AE Badhoevedorp, The Netherlands
Tel: 31-20-65-94-406 Telex: 13328 (NIKON NL) Fax: 31-20-65-98-335

NIKON INC.

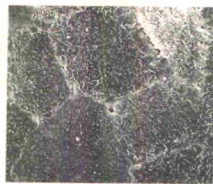
Instrument Group, Ophthalmic Instrument Division
19601 Hamilton Avenue, Torrance, CA 90502, U.S.A.
Tel: 1-800-231-3577 (Toll Free) Fax: 1-213-719-9772





Control
Phosphate-Buffered Saline*
(Preservative-Free)
• Normal morphology
• Abundant microvilli

Scanning Electron Micrographs
Of Human Corneal Epithelial Cells
Treated With Ocular Lubricants
For 60 Minutes (In Vitro-1000X
Magnification. Clinical
Significance Is Unknown)¹



Celluvisc®
Lubricant Ophthalmic Solution
(Preservative-Free)
• Normal morphology
• Abundant microvilli



Tears Naturale® II
Lubricant Eye Drops
• Compressed anterior
cell surface
• Sparse microvilli
• Some cytoplasmic pitting



HypoTears®
Lubricating Eye Drops
• Prominent rounded nuclei
• Pitted cytoplasm
• Slight cellular retraction
• Reduced number of microvilli

An advanced formulation that may help maintain epithelial cell integrity. Celluvisc Solution provides patient comfort without compromising cell morphology, cell viability, or epithelial barrier function (in vitro data, clinical significance unknown).²

Lactated Ringer's solution supplements the tears' electrolyte balance. The active ingredient, carboxymethylcellulose (CMC) 1%, has a negative charge which, along with Celluvisc Solution's high molecular weight, may promote adherence to epithelial tissue and prolong residence time.

And, Celluvisc Solution is preservative-free, thus eliminating the iatrogenic effects preservatives can cause severe dry eye patients.

Celluvisc Solution.

The serious solution for

severe dry eye associated with ocular surface disease.



Celluvisc® Lubricant Ophthalmic Solution

Contains no preservatives or EDTA.

STAGE 3
IN THE SYSTEM FOR OCULAR SURFACE DISEASE™
A Rational Plan To Manage Dry Eye Associated With Ocular Surface Disease

ALLERGAN PHARMACEUTICALS
Allergan Pharmaceuticals
A Division of Allergan, Inc.
Irvine, CA 92713 ©1991 Allergan, Inc.

WHEN SYMPTOMS ARE

SEVERE

1. Data on file, Allergan, Inc. A collaborative study with M. Trousdale, Ph.D. et al at Estelle Doheny Eye Institute.

2. Adams, J.L., Wilcox M.J., Trousdale MD et al. Morphological and physiological effects of artificial tear formulations on corneal epithelial derived cells. Invest Ophthalmol Visual Sci 1989;30 (Suppl 3):523.

Tears Naturale® and HypoTears® are registered trademarks of other companies.